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WO 01/95903 A1

(54) Title: 5-HT3 RECEPTOR ANTAGONISTS FOR TREATMENT OF DISORDERS INVOLVING AIRWAY CONSTRICTION

(57) Abstract: The present invention relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving airway constriction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

5-HT3 RECEPTOR ANTAGONISTS FOR TREATMENT OF DISORDERS INVOLVING AIRWAY CONSTRICTION

Field of the Invention

The present invention relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

Background of the Invention

The seven main receptors of the 5-HT (serotonin; 3-(β-aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported to be of significance in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in *e.g.* WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT_1 type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., *Eur. J. Pharm.*, 334, 1-23 (1997), which is incorporated herein by reference.

A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference.

SU 1 701 320 A1 discloses the use of serotonin for treatment of acute asthma attacks. This reference does not suggest any receptor mechanism for serotonin, which is a compound with both a contracting and a relaxing effect on the airways, as is further discussed herein below.

In the RBI Handbook or Receptor Classification and Signal Transduction, 3rd Edition, 1998, RBI, One

Strathmore Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling are also 5-HT receptor compounds having agonist or antagonist activity to various receptors disclosed.

Disclosure of the Invention

The present invention is based on the novel finding that certain 5-HT receptors are of utmost importance in regulating bronchocontraction, that is determining the level of airway constriction. In summary, it is disclosed herein that compounds having antagonist activity to the 5-HT_3 receptor are suitable agents in the treatment of disorders involving airway constriction. Methods for treatment of disorders involving airway constriction are also disclosed.

As used herein, the expression "disorders involving airway constriction", equivalent to the expression "bronchocontraction disorder", refers to an abnormal increase of the force development of the smooth muscle in human or animal airways, resulting in a reduced diameter in some or all of the airways of the lungs and/or the extrapulmonary airways, such as occurring in asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis. Said expression also refers, in a wider sense, to reduction of airflow, more precisely airway diameter, caused by swelling, oedema, plasma extravasation or mucous secretion caused by *e.g.* asthma or any other disorder related thereto.

The expression "has the capacity of reducing the abnormal airway constriction by at least ….%" used throughout the present patent application means that the compound in question or the composition of compounds in combination as well as the derivatives and pharmaceutically acceptable salts thereof, persistently reduces, in a certain degree, airway constriction caused either by (1) the underlying disease (asthma etc) or (2) the administration of 5-HT or other substances capable of activating constricting 5-HT receptors, e.g. 5-HT_3 receptors. The level

of constriction in the airways can, for instance, be determined by spirometric measurements of the Forced Expiratory Volume (FEV1), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

The present invention relates, in one of its aspect, to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving airway constriction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT_3 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction, wherein said antagonist has the capacity of reducing the pathological airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%.

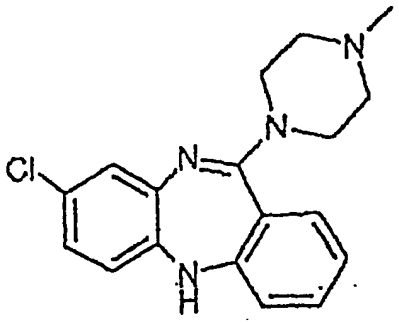
Said airway constriction may occur in conjunction with such disorders as *e.g.* asthma, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease.

According to the present invention, several known 5-HT_3 antagonist compounds are, unexpectedly, able to enhance a 5-HT-induced airway relaxation. The 5-HT_3 receptor is a ligand modulated ion channel. Several potent and specific 5-HT_3 antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial pharmaceuticals, but not against disorders involving airway constriction.

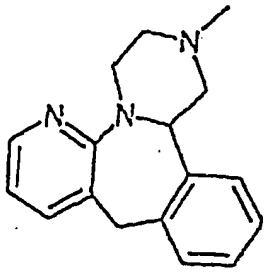
Some of the 5-HT_3 receptor antagonists are at the same time 5-HT_4 receptor agonists. However, for a substance to be active as a 5-HT_3 receptor antagonist, the distance from the aromatic center to the basic nitrogen

should be about 7,5 Å and no large substituents are tolerated on the basic nitrogen. In contrast, for 5-HT_4 receptor agonists the corresponding distance is about 8 Å, and a large lipophilic group may be bound to the basic nitrogen, thereby obtaining a better binding to 5-HT_4.

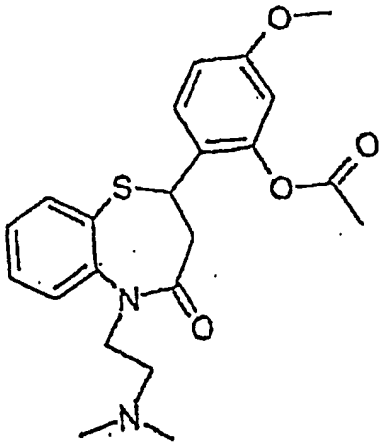
The 5-HT_3 antagonists may be divided into certain classes on the basis of chemical structure. Some are unspecific, e.g.



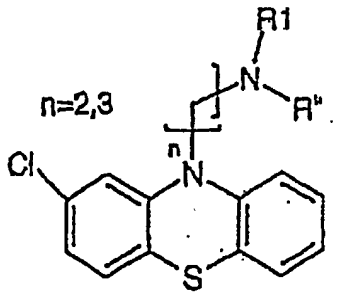
benzazepines, e.g. mirtazapine



benztiazephines, e.g. diltiazem

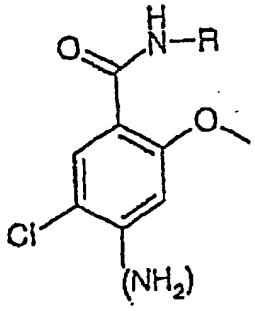


and fentiazines



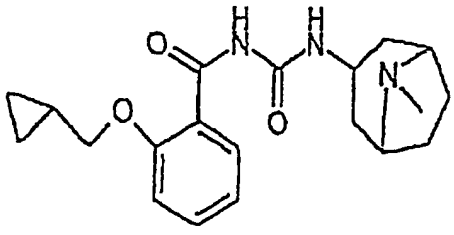
e.g. perphenazine, chlorpromazine, stemetil.

Some are at the same time 5-HT_4 agonists, e.g. benzamides



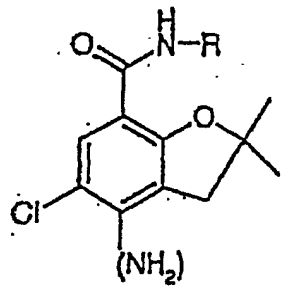
(cisapride, zacopride, mosapride, metoclopramide, pancopride, BRL 24924, BMY 33462)

and

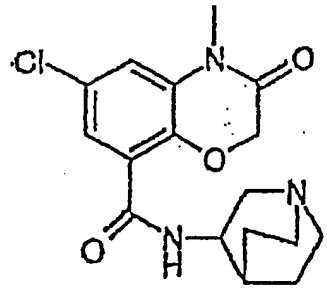


WAY 100289

2,3-dihydro-benzofuran-7-carboxamides

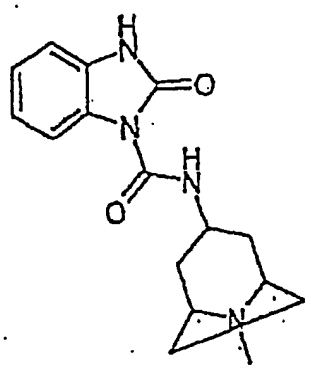


(e.g. zatosetron=LY 277359, ADR 851);
1,4-bensoxazin-8-carboxamides



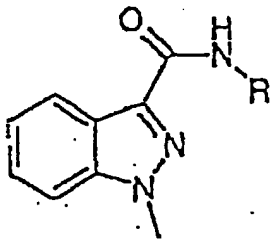
e.g. azasetron (=Y25130)

benzimidazolones



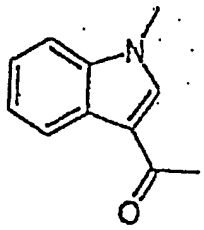
e.g. itasetron (=DAU 6215);

indazol-3-carboxamides

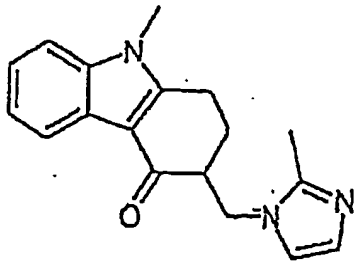


e.g. N 3389, LY 278584, DAT 582 (=(R)AS-5370)

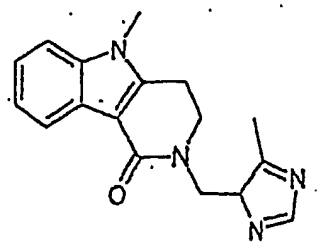
The latter group reminds most of the specific 5-HT_3 antagonists, which contains the group



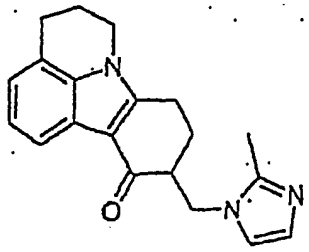
in different forms, such as



ondansetron (=GR 38032 F)

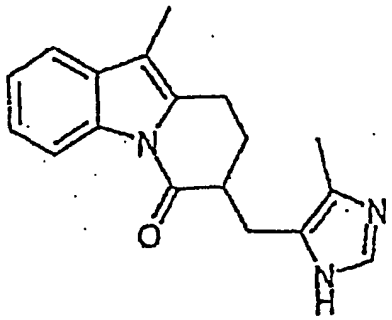


alosetron



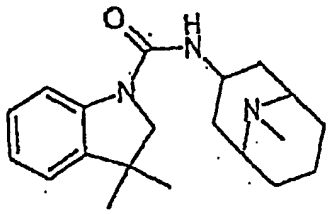
cilansetron (=KC 9946)

In one group of substances the structure has been inverted and the carbonyl group has been placed on the indoline nitrogen



FK 1052

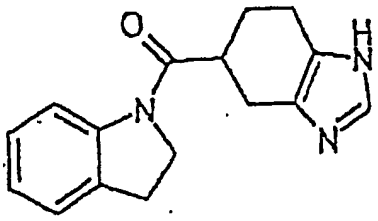
This substance is unique by being an antagonist against both 5-HT_3 and 5-HT_4 receptors.



BRL 46470 A

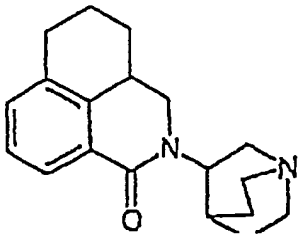
BRL 46470A binds to two different positions of the receptor.

A further development is the so-called bisindoles

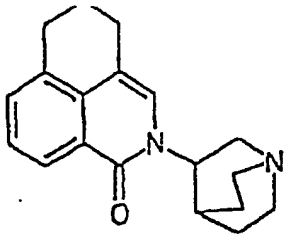


YM 114

Another group is the isoquinoline-1-ones

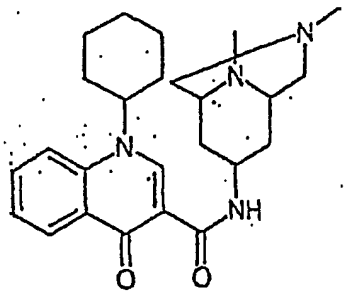


palonosetron (=RS 25259-197)

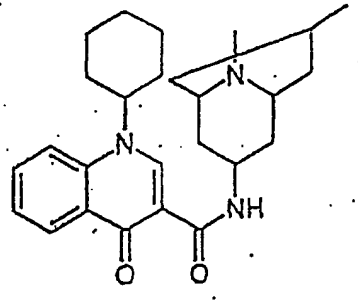


RS 42358-197

and the quinoline-3-carboxamides

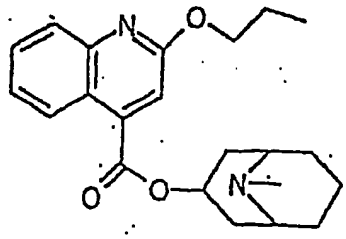


WAY-SEC 579

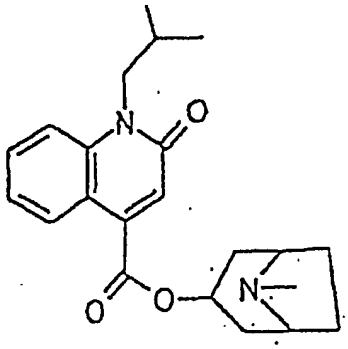


Mirisetron (=WAY 100579)

Also the quinoline-4-carboxylates are active antagonists

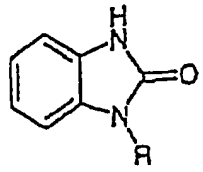


e.g. KF 17643

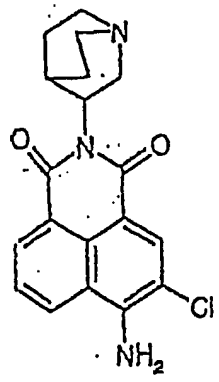


e.g. KF 18259

Other compounds are benzimidazolones



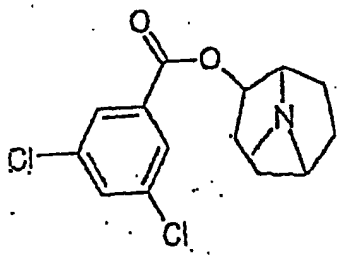
e.g. droperidol (neurolidol, etc.), itasetron (DAU6215), and the naphtimides



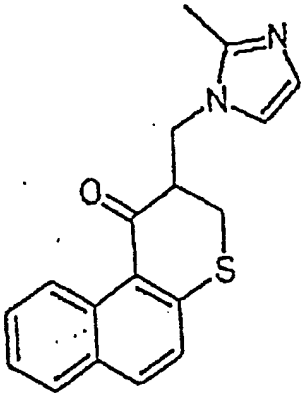
RS 56532

e.g. RS 56532

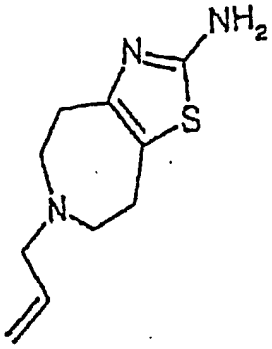
A unique single structure is MDL 72222, which also is a specific 5-HT_3 antagonist



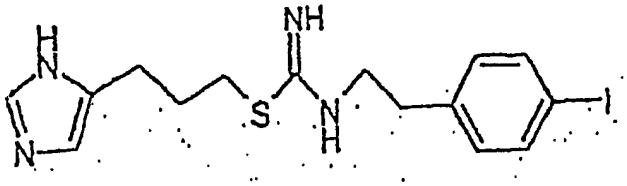
Other specific structures are



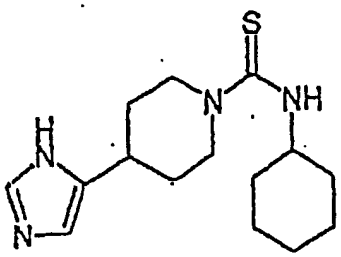
GK 128



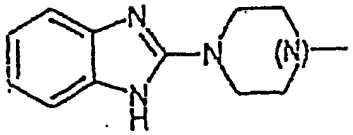
Talipexole



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles.

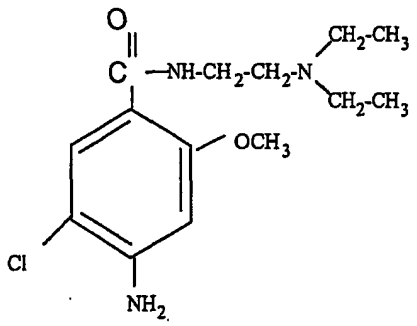
According to the present invention, the following compounds can also be used as antagonists to the 5-HT_3 receptor: (R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKI-48903, ICS 205-930, Imipramine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Pancopride, Phenylbiguanide, Pitozifen, Prochlorperazine (Stemetil), QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-25259-197, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-

apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron (=ICS 205-930=Rifenserin), Bemesetron, L-683,877, LY-278,584 maleate and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect and capability of reducing abnormal airway constriction as specified above.

In the following, an alternative presentation of useful compounds according to the present invention and references thereto is presented.

N-substituted benzamides

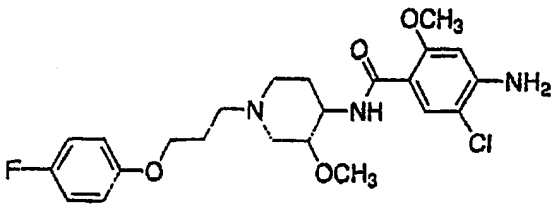
- Metoclopramide



- QX 222. The compound is an analogue to lidocain®, which is a N-substituted benzamide derivative.

- Cisapride (Cizapride) cis-4-Amino-N-[1-[3-(p-fluorophenoxy)propyl]-3-methoxy-4-piperidyl]-5-chloro-o-anisamide. The compound is also a known 5-HT4 agonist.

cis-4-Amino-*N*-[1-[3-(*p*-fluorofenoxi)propyl]-3-metoxi-4-piperidyl]-5-kloro-*o*-anisamid



- Pancopride (((+-)N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide)

Pancopride, a potent and long-acting 5-HT3 receptor antagonist, is orally effective against anticancer drug-evoked emesis., Fernández AG, Puig J, Beleta J, Doménech T, Bou J, Berga P, Gristwood RW, Roberts DJ; *Eur J Pharmacol* 1992 Nov 10, 222:2-3:257-64

Pancopride ((+-)N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-ami no-5-chlorobenzamide) is a new potent and selective 5-HT3 receptor antagonist, orally and parenterally effective against cytotoxic drug-induced emesis. In vitro, pancopride displayed high affinity (Ki = 0.40 nM) for [3H]GR65630-labelled 5-HT3 recognition sites in membranes from the cortex of rat brains. In vivo, pancopride antagonized 5-HT-induced bradycardia in anaesthetized rats when administered i.v. 5 min (ID50 = 0.56 microgram/kg) or p.o. 60 min (ID50 = 8.7 micrograms/kg) before 5-HT challenge. A single oral dose (10 micrograms/kg) of pancopride produced a signifi-

cant inhibition of the bradycardic reflex over an 8-h period. Pancopride dose dependently inhibited the number of vomiting episodes and delayed the onset of vomiting induced by cisplatin in dogs (ID50 = 3.6 micrograms/kg i.v. and 7.1 micrograms/kg p.o.). Pancopride was also effective in blocking mechlorethamine- and dacarbazine-induced emesis. Unlike metoclopramide, pancopride was shown to lack any measurable antidopaminergic activity both in vitro and in vivo. These results support clinical data, indicating that pancopride will be a useful drug for treating cytostatic-induced emesis in humans. -

- (R)-zacopride (R+ zacopride, zacopride) IUPAC name: 4-amino-N-(1-azabicyclo[2.2.2] oct-3yl)-5-chloro-2-methoxy-benzamide.

The differential activities of R (+)- and S(-)-zacopride as 5-HT3 receptor antagonists.
Barnes JM, Barnes NM, Costall B, Domeney AM, Johnson DN, Kelly ME, Munson HR, Naylor RJ, Young R; *Pharmacol Biochem Behav* 1990 Dec, 37:4:717-27

R(+)- and S(-)-zacopride were assessed as potential 5-HT3 receptor antagonists in behavioural and biochemical tests. The S(-)isomer was more potent than the R(+)isomer to antagonise the hyperactivity induced by the injection of amphetamine or the infusion of dopamine into the nucleus accumbens in the rat. In contrast, the R(+)isomer was more potent to reduce the aversive behaviour of mice to a brightly illuminated environment and in a marmoset human threat test, to facilitate social interaction in rats, to increase performance in a mouse habituation test and prevent a scopolamine-induced impairment, and to antagonise the inhibitory effect of 2-methyl-5-hydroxytryptamine to reduce [3H]acetylcholine re-

lease in slices of the rat entorhinal cortex. In binding assays, [3H]S(-)-zacopride and [3H]R(+)-zacopride labelled homogenous populations of high-affinity binding sites in the rat entorhinal cortex, R(+)-zacopride compete for a further 10 to 20% of the binding of [3H]R(+)/S(-)-zacopride or [3H]R(+)-zacopride in excess of that competed for by (S)(-)-zacopride. It is concluded that both isomers of zacopride have potent but different pharmacological activities, with the possibility of different recognition sites to mediate their effects.

- BRL 24682
  The compound is also a known 5-HT4 agonist.

- BRL 24924
  [(+/-)- (endo)])-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo-[3.3.1]-non- 4-yl) benzamide hydrochloride. The compound is also a known 5-HT4 agonist.

- Mosapride ((4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl] benzamide citrate.

- Renzapride= BRL 24924; see above

- SC-52491 (Azanoradamantane)

- SC-53116 ((1-S,8-S)-4-amino-5-chloro-N-[(hexahydro-1H-pyrrolizin-1-yl) methyl]-2-methoxy-benzamide hydrochloride)

- Batanopride (4-amino-5-chloro-N-[2-(diethylamino)-ethyl]2-(1-methyl-2-oxopropoxy) benzamide). Batanopride is also known by the name BMY-25801.

- WAY 100289

Indoles, Indole-1-carboxamides and Imidazole derivatives

- 2-methyl-5-HT
- 5,7-DHT= 5,7-dihydroxy-tryptamine
- Bisindoles
- Bufotenine =(5-hydroxy-N,N-dimethyltryptamine)
- BRL 46470A (endo-N-(8-methyl-8-azabicyclo [3.2.1]oct-3-yl)2,3-dihydro-3,3 dimethyl-indole-1-carboxamide, hydrochloride)
- BRL 46470 (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl)
- BRL 47204
- FK 1052 ((+)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4- yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride)

Pharmacological characterization of FK1052, a dihydropyridoindole derivative, as a new serotonin 3 and 4 dual receptor antagonist., Nagakura Y, Kadowaki M, Tokoro K, Tomoi M, Mori J, Kohsaka M; *J Pharmacol Exp Ther* 1993 May, 265:2:752-8

(+)-8,9-Dihydro-10-dihydro-10-methyl-7-[(5-methyl-4-imidazolyl) methyl]pyrido-[1,2-a]indol-6(7H)-one hydrochloride (FK1052) is a newly designed and synthesized 5-hydroxytryptamine (5-HT)3 receptor antagonist with 5-HT4 receptor antagonistic activity. This compound, as well as ondansetron and granisetron,

dose-dependently inhibited the von Bezold-Jarish reflex, a 5-HT3 receptor-mediated response, after intravenous (i.v.) and intraduodenal (i.d.) dosing to rats. The ID50 values showed FK1052 (0.28 microgram/kg, i.v., 5.23 micrograms/kg, i.d.) to be more potent than ondansetron (5.23 micrograms/kg, i.v., 170 micrograms/kg, i.d.) and granisetron (0.70 micrograms/kg, i.v., 66 micrograms/kg, i.d.). Furthermore, bioavailabilities of the test drugs by ID50 ratio (i.d./i.v.) showed that FK1052(17) was better absorbed than ondansetron(33) and granisetron(94) and possessed a similar duration of action to that of ondansetron and granisetron. We also examined the effects on 2-methyl-5-HT-, 5-HT- and 5-methoxytryptamine-induced contractions of guinea pig isolated ileum. FK1052, ondansetron and granisetron concentration-dependently inhibited 2-methyl-5-HT, a 5-HT3 agonist-induced contraction. The pA2 values for the 5-HT3 receptor indicated that FK1052 (8.36) was 40 times and three times more potent than ondansetron (6.79) and granisetron (7.86), respectively. FK1052, unlike ondansetron and granisetron, inhibited the 5-HT4-mediated component of concentration-response curve to 5-HT. Furthermore, FK1052 suppressed 5-methoxytryptamine, a 5-HT4 agonist-induced contraction in a concentration-dependent but insurmountable manner.

- RU 24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)-1 H-indole)

- SDZ 206-792

Characterisation of 5-HT3 recognition sites in membranes of NG 108-15 neuroblastoma-glioma cells with [3H]ICS 205-930. Neijt HC, Karpf A, Schoeffter P,

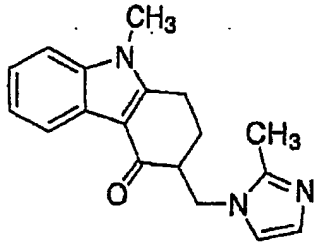
Engel G, Hoyer D Naunyn Schmiedebergs *Arch Pharmacol* 1988 May, 337:5:493-9

1. The binding characteristics of [3H]ICS 205-930, a potent and selective 5-hydroxytryptamine 5-HT3 receptor antagonist, were investigated in membranes prepared from murine neuroblastoma-glioma NG 108-15 cells. 2. [3H]ICS 205-930 bound rapidly, reversibly and stereoselectively to a homogeneous population of high affinity recognition sites: Bmax = 58 +/- 3 fmol/mg protein, pKD = 9.01 +/- 0.08 (n = 11). Non linear regression and Scatchard analysis of saturation data suggested the existence of a single class of [3H]ICS 205-930 recognition sites on NG 108-15 cells. The binding was rapid, stable and reversible. The affinity of [3H]ICS 205-930 determined in kinetic studies was in agreement with that obtained under equilibrium conditions. 3. Competition studies performed with a variety of agonists and antagonists also suggested the presence of a homogeneous population of [3H]ICS 205-930 recognition sites. All competition curves were steep and monophasic and were best fit by a 1 receptor site model. [3H]ICS 205-930 binding sites displayed the pharmacological profile of a 5-HT3 receptor. Potent 5-HT3 receptor antagonists showed nanomolar affinities for [3H]ICS 205-930 binding sites with the following rank order of potency: SDZ 206-830 greater than ICS 205-930 greater than SDZ 206-792 greater than BRL 43694 greater than quipazine greater than BRL 24924 greater than SDZ 210-204 greater than MDL 72222 greater than SDZ 210-205. Metoclopramide, mCP and mianserin showed submicromolar affinity.

- Ondansetron=GR 38032F=SN-307=Zofran®

Ondansetronum INN (Ondansetron)

2,3-Dihydro-9-metyl-3-[(2-metylimidazol-1-yl)metyl]karbazol-4(1*H*-on



The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.

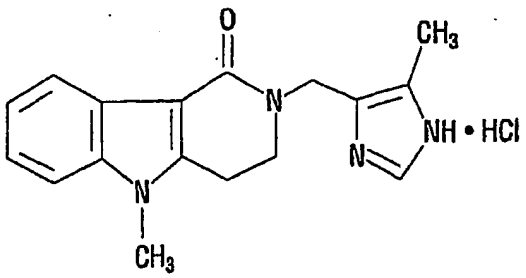
- GR 38032 F

  Comparison of the 5-HT3 receptor antagonist properties of ICS 205-930, GR38032F and zacopride.,Cohen ML, Bloomquist W, Gidda JS, Lacefield W; *J Pharmacol Exp Ther* 1989 Jan, 248:1:197-201

  The well-documented 5-HT3 receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT3 receptors to another gastrokinetic agent, zacopride. Zacopride and ICS 205-930 showed similar affinity (-log kB approximately 8.0), whereas GR38032F showed lower affinity (-log ka approximately 7.0) at 5-HT3 receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT3-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent

than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT3 receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less potent than ICS 205-930 and possessed the shortest duration of action.

- Alosetron=Lotronex (Glaxo)



The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.

The pharmacological properties of the novel selective 5-HT3 receptor antagonist, alosetron, and its effects on normal and perturbed small intestinal transit in the fasted rat., Clayton NM, Sargent R, Butler A, Gale J, Maxwell MP, Hunt AA, Barrett VJ, Cambridge D, Bountra C, Humphrey PP; *Neurogastroenterol Motil* 1999 Jun, 11:3:207-17

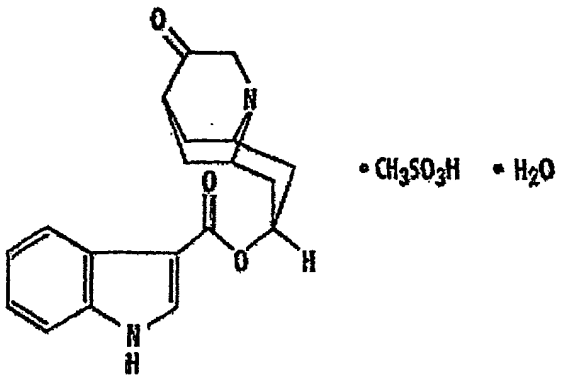
The purpose of this study was to investigate the pharmacological properties of the novel, selective 5-HT3 receptor antagonist, alosetron, and its effects on transit time in both the normal and perturbed small intestine of the rat. Alosetron concentration-dependently inhibited radioligand binding in membranes containing rat and human 5-HT3 receptors with estimated pKi values of 9.8 (n = 3) and 9.4 (n = 6), respectively. In selectivity studies alosetron had little or no significant affinity for any of the many other receptors and ion channels studied. Alosetron potently antagonized the depolarization produced by 5-HT in the rat vagus nerve (estimated pKB value of 9.8, n = 25). In anaesthetized rats, i. v. administration of alosetron inhibited 2-methyl-5-HT induced bradycardia (Bezold Jarisch index) at 1 and 3 microg kg-1, with an agonist dose ratio of approximately 3.0 at 1.0 microg kg-1, = 3-5). Alosetron administered via the duodenum also inhibited this reflex, with duration of action that was significantly longer than that seen with ondansetron (120-60 min, respectively, n = 6). Alosetron had no significant effect on normal small intestinal propulsion in the rat, but fully reversed the increase in intestinal propulsion (96%, n = 3) produced by egg albumin challenge. Alosetron is a highly selective 5-HT3 antagonist which normalizes

perturbed small intestinal propulsion. Previous clinical data in IBS patients together with the transit data provide a good rationale for further studies with alosetron in IBS patients.

- Bemesetron

- Galdansetron

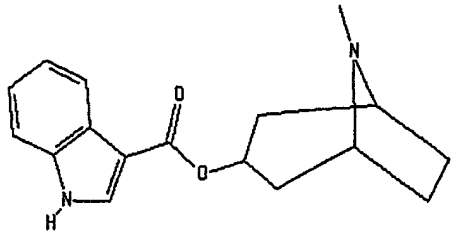
- Dolasetron mesilat =MDL73147 EF= Anzemet.
  IUPAC name: (2,6,8,9aß)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate, monohydrate.



- Dolasetron=MDL74156

- Tropisetron =Navoban®

  IUPAC name: 1aH,5aH - Tropane - 3a - yl-3 - indole-carboxylate



- Zatosetron =LY 277359. The compound is also called LY 19617.

The effect of acute and chronic LY 277359, a selective 5-HT3 receptor antagonist, on the number of spontaneously active midbrain dopamine neurons., Minabe Y, Ashby CR Jr, Wang RY; *Eur J Pharmacol* 1991 Dec 17, 209:3:151-6

In this study, we have examined the effect of acute and chronic administration of LY 277359, a putative 5-HT3 receptor antagonist, on the number of spontaneously active dopamine cells in the substantia nigra pars compacta (SNC or A9) and ventral tegmental area (VTA or A10). This was accomplished using the standard extracellular single unit recording techniques. The acute administration of LY 277359 (0.1 or 1.0 mg/kg i.p.) produced a significant increase in the number of spontaneously active A10, but not A9, dopamine cells compared to saline controls. The acute administration of 10 mg/kg of LY 277359 did not significantly alter the number of spontaneously active dopamine cells in either area. In contrast to

its acute effects, the administration of 0.1 mg/kg per day of LY 277359 for 21 days decreased the number of spontaneously active A9 and A10 dopamine cells. However, the i.v. administration of (+/-)-apomorphine (50 micrograms/kg) did not reverse LY 277359's action, suggesting that the chronic LY 277359-induced reduction of dopamine cells was not the result of depolarization block. To test whether chronic administration of LY 277359 at a high dose would induce depolarization block of dopamine cells, rats were treated with 1.0 or 10 mg/kg LY 277359. Interestingly, the chronic administration of - 1.0 mg/kg LY 277359 increased the number of A10, but not A9 dopamine cells. In contrast, chronic treatment with 10 mg/kg selectively decreased the number of spontaneously active A10 dopamine cells.

- GR65630 (3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1- propanone)

- GR67330
  [3H] GR67330, a very high affinity ligand for 5-HT3 receptors.
  Kilpatrick GJ, Butler A, Hagan RM, Jones BJ, Tyers MB Naunyn Schmiedebergs *Arch Pharmacol* 1990 Jul, 342:1:22-30

  GR67330 potently inhibited 5-hydroxytryptamine (5-HT)-induced depolarizations of the rat isolated vagus nerve. At the higher concentrations used (0.3 nmol/l-1 nmol/l) this was accompanied by a marked reduction in the maximum response to 5-HT. The calculated pKB value was 10.2. The binding of the tritiated derivative of GR67330 to homogenates of rat entorhinal cortex was examined. Kinetic analysis revealed that specific [3H] GR67330 (0.1 nmol/l) binding was rapid and reversible. Association and disso-

ciation rate constants were 1.48 +/- 0.36 x 10(8) mol/l-1 s-1 and 7.85 +/- 0.41 x 10(-3) s-1 respectively. Equilibrium saturation analysis revealed specific binding was to a single site (Bmax 22.6 +/- 0.21 fmol/mg protein) of high affinity (Kd 0.038 +/- 0.003 nmol/l). At low ligand concentrations, specific binding was up to 90% of total binding. If unlabelled GR67330 was used to define non-specific binding two sites were evident (Kd1 0.066 +/- 0.007 nmol/l, Kd2 20.1 +/- 9.7 nmol/l; Bmax1 31.5 +/- 3.2 fmol/mg protein, Bmax2 1110 +/- 420 fmol/mg protein). [3H] GR67330 binding was inhibited potently by 5-HT3 antagonists and agonists. Ligands for other 5-HT receptors and other neurotransmitter receptors were either only weakly active or inactive at inhibiting binding. Hill numbers for antagonist inhibition of binding were close to unity, except for quipazine which was significantly greater than one. In common with other 5-HT3 binding studies, all 5-H-agonist tested had Hill numbers greater than one (1.51-1.71). GR38032 and GR65630 inhibited a greater proportion of binding than other 5-HT3 antagonists, this additional binding was interpreted as inhibition from a second saturable site unrelated to the 5-HT3 receptor.

- ICS 205-930 ((3 Alpha-Tropanyl)-1H-Indole-3-carboxylic acid ester)
  Comparison of the 5-HT3 receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W
  J Pharmacol Exp Ther 1989 Jan, 248:1:197-201

  The well-documented 5-HT3 receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT3 receptors to another gastrokinetic agent, zacopride. Zacopride

and ICS 205-930 showed similar affinity (-log kB approximately 8.0), whereas GR38032F showed lower affinity (-log ka approximately 7.0) at 5-HT3 receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT3-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT3 receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less potent than ICS 205-930 and possessed the shortest duration of action.

- QICS 205-930

- 3-Tropanyl-indole-3-carboxylate methiodide. It is also called ICS 205-930.

- Indalpine (3-[2-(4-piperidinyl)ethyl]-1H-indole)

- VA21B7 (3-[2-(4'-piperonylpiperazinyl) indolyl] carboxaldehyde)

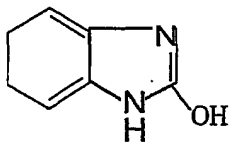
The pharmacology of VA21B7: an atypical 5-HT3 receptor antagonist with anxiolytic-like properties in animal models. Artaiz I, Romero G, Zazpe A, Monge A, Calderó JM, Roca J, Lasheras B, Del Río J *Psychopharmacology* (Berl) 1995 Jan, 117:2:137-48

VA21B7 (3-[2-(4'-piperonylpiperazinyl) indolyl] carboxaldehyde) was synthesized as a potential 5-HT3 receptor antagonist. Even though VA21B7 showed a higher affinity towards 5-HT3 receptors as compared to other receptors studied, it was not a potent 5-HT3 receptor antagonist either in the periphery or in the brain. In a simple animal model of anxiety such as the two-compartment box in mice, a remarkable anxiolytic-like effect was found at doses of 2-500 micrograms/kg IP and also at low oral doses, in the microgram range. These drug doses did not produce any significant effect on spontaneous motor activity of mice. The anxiolytic profile of VA21B7 was further explored using other models of anxiety in rats such as the elevated plus-maze and punished-drinking. VA21B7 was compared with standard 5-HT3 receptor antagonists such as ondansetron, tropisetron and granisetron, with the 5-HT1A agent buspirone and with diazepam. In the plus-maze, VA21B7 showed an anxiolytic-like profile after doses of 0.25-0.5 mg/kg IP or 2-4 mg/kg PO which did not modify the number of total entries into the open and closed arms of the maze. Diazepam, granisetron and

tropisetron were also effective in this test but not ondansetron and buspirone. VA21B7 was also able to release suppressed behaviour in the punished-drinking test. The dose-response curve was bell-shaped with a peak at 2-4 mg/kg. At variance with other studies, 5-HT3 receptor antagonists also increased the number of shocks taken in this test and the dose-response curve was also bell-shaped. VA21B7 was not anticonvulsant like diazepam, its anxiolytic action in the light/dark test was not flumazenil-sensitive and there was no rebound anxiogenic effect on withdrawal from chronic VA21B7 treatment for 15 consecutive days. Moreover, VA21B7 was not amnesic like the benzodiazepines but low doses of 2-4 mg/kg reduced the memory deficits induced in rats by scopolamine. Much higher doses were necessary to decrease spontaneous motor activity in rats. Since VA21B7 appears to be well tolerated in rodents at high doses, we think that it is of potential interest as an anxiolytic in humans.

Benzimidazolones, benzimidazoles and other imidazoles

The common chemical structure of a benzimidazolone is:



- Iodophenpropit (4-(1H-imidazol-4-yl-methyl)-piperidine)

- BIMU 1 (endo-N-(8-methyl-8-azabicyclo[3.2.1.]oct-3-yl)- 2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride)

- 2-piperazin-benzimidazole

- 2-piperidin-benzimidazole

- Cilansetron (1-10-[(2-methyl-1H-imidazol-1-yl)methyl]-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk]carbazol-11-one hydrochloride)

- GK 128 (2-[(2-methylimidazol-1-yl)methyl]benzo[i]-thiochromen-1-one monohydrochloride hemihydrate
Effect of a novel 5-hydroxytryptamine3 (5-HT3) receptor antagonist, GK-128, on 5-HT3 receptors mediating contractions and relaxations in guinea-pig distal colon.
Ito C, Kawamura R, Isobe Y, Tsuchida K, Muramatsu M, Higuchi S;
Gen Pharmacol 1997 Sep, 29:3:353-9

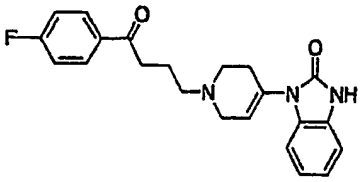
We investigated 5-hydroxytryptamine3 (5-HT3) receptor-mediating contractions and relaxations in the guinea-pig isolated distal colon using various 5-HT3 receptor agonists and antagonists, including GK-128 (2-[(2-methylimidazol-1-yl) methyl] benzo[f] thiochromen-1-one monohydrochloride hemihydrate). 2.Selective 5-HT3 receptor agonists, 2-methyl-5-HT and m-chlorophenylbiguanide, produced spantide-insensitive contraction and atropine-insensitive contraction and the relaxation. These agonists showed a small, but significant, difference of potency between contraction and relaxation. 3. GK-128 competitively blocked both 2-methyl-5-HT- and m-chlorophenylbiguanide-induced responses with similar potency. The affinities of GK-128 for spantide-insensitive contraction and atropine-insensitive contraction were ten-fold higher than for relaxation. 4. Other selective 5-HT3 receptor antagonists, azasetron and tropisetron, also exhibited higher af-

finity in contraction than in relaxation, but the extent of their affinity differences was smaller than that observed in GK-128. In contrast, granisetron, ramosetron and ondansetron exhibited no significant differences in their affinity values among the three responses. 5. These results suggest that the 5-HT3 receptors which mediate contraction and relaxation in the guinea-pig distal colon may not be the same, and that GK-128 is a 5-HT3 receptor antagonist with a stronger potency for contraction.

- Droperidol. Ingår i Dridol, Janssen-Cilag

Droperidolum INN (Droperidol)

1-[1-(3-(4-Fluorobensoyl)propyl)-1,2,3,6-tetrahydro-4-pyridyl]-1,3-dihydro-2*H*-bensimidazol-2-on



- KAE-393/YM-114
((R)-5-[(2,3-dihydro-1-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole

Comparison of the effects of trimebutine and YM114 (KAE-393), a novel 5-HT3 receptor antagonist, on stress-induced defecation. Miyata K, Ito H, Yamano M, Hidaka K, Kamato T, Nishida A, Yuki H; *Eur J Pharmacol* 1993 Dec 7, 250:2:303-10

YM114 (KAE-393), (R)-5-[(2,3-dihydro-1-indolyl)-carbonyl]-4,5,6,7- tetrahydro-1H-benzimidazole hydrochloride, is a derivative of YM060, a potent 5-

HT3 receptor antagonist. We investigated the effects of YM114 on 5-HT3 receptors, both in vitro and in vivo, and on bowel dysfunction induced by restraint stress, 5-HT and thyrotropin-releasing hormone (TRH), and compared them with the effect of trimebutine. YM114 dose dependently inhibited the reduction in heart rate induced by 5-HT (30 micrograms/kg i.v.) in rats (ED50 = 0.31 micrograms/kg i.v.), and the potency of YM114 was almost the same as that of the racemate. The S-form of YM114 also inhibited 5-HT-induced bradycardia, but 1350 times less potent than the R-form. YM114 and its S-form inhibited [3H]GR65630 binding to N1E-115 cell membranes in a concentration-dependent manner with Ki values of 0.341 and 616 nM, respectively, showing the isomeric activity ratio (R-/S-form) of YM114 to be much greater (1800). YM114 antagonized 5-HT-induced depolarization of the nodose ganglion (EC50 = 1.39 nM). Trimebutine (1 mg/kg i.v.) failed to inhibit 5-HT-induced bradycardia, implying that it does not possess 5-HT3 receptor antagonistic activity. YM114 significantly and dose dependently prevented restraint stress-, 5-HT- and TRH-induced increases in fecal pellet output, and restraint stress- and 5-HT-induced diarrhea in rats and mice (ED50 = 6.9, 72.5, 154.6, 9.7 and 52.4 micrograms/kg p.o., respectively). Trimebutine significantly prevented stress- and 5-HT-induced diarrhea (ED50 = 29.4 and 87.3 mg/kg p.o., respectively), but only partially affected stress-, 5-HT- and TRH-induced increases in fecal pellet output. Thus, YM114 is a potent and stereoselective 5-HT3 receptor antagonist with much greater protective effects against stress-induced defecation than trimebutine.hydrochloride).

- Itasetron=DAU6215 ((3-alpha-tropanyl)1H-benzimidazolone-3-carboxamide chloride)

Intravenous itasetron: establishing the effective dose range for the prophylactic control of acute emesis in cancer patients undergoing high-dose cisplatin chemotherapy., Patoia L, Del Favero A, Giglietti A, Malacarne P, Donati D, Indelli M, Bensi G, Palladino MA, Cigarini P, Kempe R, Voigt T; *Clin Oncol* (R Coll Radiol) 1999, 11:2:99-104

Nausea and vomiting induced by chemotherapy are a major cause of distress to patients and reduce compliance with potentially beneficial treatment. Itasetron hydrochloride is a new 5-hydroxytryptamine3 (5-HT3) antagonist with potent antiemetic properties. It is more potent than ondansetron in animal models and in early clinical studies it demonstrates a long half-life and does not undergo hepatic biotransformation before elimination. The aim of this open, uncontrolled study was to establish the effective dose range of itasetron hydrochloride given intravenously (i.v.) to patients due to receive high-dose cisplatin chemotherapy (50-120 mg/m2) for the first time. Thirty-nine patients were enrolled in the trial and received a single i.v. infusion of itasetron hydrochloride at a dose of 17-280 microg/kg body weight before commencing the cisplatin infusion (median dose 90-110 mg/m2). Antiemetic protection was demonstrated by doses in the range of 35-280 microg/kg. The 17 microg/kg dose was not effective. Treatment failure (>5 emetic episodes/24 hours) was reported in only six (16%) of the 38 evaluable patients over all treatment groups. Adverse events were generally mild or moderate and of a similar type and incidence to those of current 5-HT3 antagonists. Physicians' and patients' assessments of efficacy and tolerability of itasetron hydrochloride were similar, the majority rating the treatment as 'good' or 'very good'. In conclusion,

itasetron hydrochloride is effective in the dose range 35-280 microg/kg in preventing cisplatin-induced emesis. Taken together with results from a larger dose-finding study, a dose corresponding to 35 microg/kg (equivalent to 2.5 mg itasetron, calculated as free base) has been pursued in Phase III studies with the i.v. formulation.

- Lerisetron

New 2-piperazinylbenzimidazole derivatives as 5-HT3 antagonists. Synthesis and pharmacological evaluation. Orjales A, Mosquera R, Labeaga L, Rodes R *J Med Chem* 1997 Feb 14, 40:4:586-93

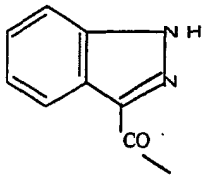
A series of 2-piperazinylbenzimidazole derivatives were prepared and evaluated as 5-HT3 receptor antagonists. Their 5-HT3 receptor affinities were evaluated by radioligand binding assays, and their abilities to inhibit the 5-HT-induced Bezold-Jarisch reflex in anesthetized rats were determined. Compound 7e (lerisetron, pKi = 9.2) exhibited higher affinity for the 5-HT3 receptor than did tropisetron and granisetron, while compound 7q (pKi = 7.5) had very low affinity for this receptor, showing that substitution on the N1 atom of the benzimidazole ring is essential for affinity and activity. The effect of substitution on the aromatic ring of benzimidazole by several substituents in different positions is also discussed. A strong correlation between the 5-HT3 antagonistic activity of the studied compounds and the position of substitution on the aromatic ring was established. Thus, while the 4-methoxy derivative 7m showed weak affinity for the 5-HT3 receptor (pKi = 6.7), the 7-methoxy derivative 7n exhibited the highest affinity (pKi = 9.4). Compounds 7e and 7n are now under further investigation

as drugs for the treatment of nausea and emesis evoked by cancer chemotherapy and radiation.

- Lurosetron
- Mirisetron =WAY100579
- Ramosetron =YM 060. [(R)-5-[(1-methyl-3-indolyl)-carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole hydrochloride]

Indazole carboxamide derivatives

The compounds have the general structure.



- AS5370 ((+/-)-N-[1-methyl-4-(3-methyl-benzyl)-hexahydro-1H-1,4-diazepin-6- yl]-1H- indazole-3-carboxamide dihydrochloride). The compound is also a diazepin derivative.
- DAT582 (the compound is the R- enantimer of compound AS5370)

5-HT3 receptor antagonist effects of DAT-582, (R) enantiomer of AS-5370.
Yoshida N, Omoya H, Kato S, Ito T, *Eur J Pharmacol* 1992 Jun 17, 216:3:435-40

The serotonin 5-HT3 receptor antagonist effects of DAT-582, the (R) enantiomer of AS-5370 ((+/-)-N-[1-methyl-4-(3-methyl-benzyl)hexahydro-1H-1,4-diazepin-

6- yl]-1H- indazole-3-carboxamide dihydrochloride), and its antipode were compared with those of AS-5370 and existing 5-HT3 receptor antagonists. In anesthetized rats, DAT-582 antagonized 2-methyl-5-HT-induced bradycardia with an ED50 value of 0.25 microgram/kg i.v., whereas the (S) enantiomer was without effect even at 1000 micrograms/kg i.v. In antagonizing the bradycardia, DAT-582 was as potent as granisetron, slightly more potent than AS-5370, and 2, 5 and 18 times more potent than ondansetron, ICS 205-903 and renzapride, respectively, although it was less potent than zacopride. DAT-582 inhibited cisplatin (10 mg/kg i.v.)-induced emesis in ferrets with an ED50 value of 3.2 micrograms/kg i.v. twice. The antiemetic activity of DAT-582 was more potent than that of the existing 5-HT3 receptor antagonists examined, except zacopride. In contrast, the (S) enantiomer had little effect at 1000 micrograms/kg i.v. twice. In isolated guinea-pig ileum, DAT-582 inhibited 5-HT-induced contractions with an IC50 value of 91 nM, whereas the (S) enantiomer hardly inhibited them even at 1000 nM. These results suggest that DAT-582, the (R) enantiomer of AS-5370, potently and selectively blocks 5-HT3 receptors.

- N-3389 (N-3389 (endo-3,9-dimethyl-3,9- diazabicyclo[3,3,1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride)

Antagonistic activities of N-3389, a newly synthesized diazabicyclo derivative, at 5-HT3 and 5-HT4 receptors., Hagihara K, Hayakawa T, Arai T, Eguchi H, Mino S, Kawase S, *Eur J Pharmacol* 1994 Dec 12, 271:1:159-66

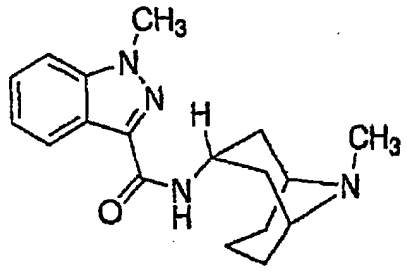
The antagonistic activities of compound N-3389 (endo-3,9-dimethyl-3,9- diazabicyclo[3,3,1]non-7-yl

1H-indazole-3-carboxamide dihydrochloride) at 5-HT3 and 5-HT4 receptors were examined using in vitro and in vivo assays. N-3389 showed potent 5-HT3 receptor antagonistic activities in a radioligand binding assay (pKi = 8.77), against 2-methyl-5-HT (2-Me-5-HT)-induced bradycardia in rats (ED50 = 0.73 micrograms/kg i.v., 38 micrograms/kg p.o.) and against 2-Me-5-HT-induced contraction in longitudinal muscle myenteric plexus preparations of guinea-pig ileum (IC50 = 3.2 x 10(-8) M). As a preliminary to investigating the effect of N-3389 on 5-HT4 receptors, we examined the contraction induced by 5-HT in guinea-pig ileum preparations. We confirmed that 5-HT (10(-8)-10(-5) M) induced biphasic contractions in the preparations. Furthermore, 5-HT3 receptor antagonism inhibited the late phase of the contraction induced by high concentrations of 5-HT (3 x 10(-6)-10(-5) M), whereas 5-HT4 receptor antagonism inhibited the early phase of the contraction induced by low concentrations of 5-HT (10(-8)-10(-6) M). N-3389 (10(-7)-10(-5) M) inhibited both phases of contraction induced by 5-HT. In addition, N-3389 (3 x 10(-7)-3 x 10(-6) M) was found to inhibit the increase of electrically stimulated twitch responses induced by 5-HT (10(-8) M) longitudinal muscle myenteric plexus preparation of the guinea-pig ileum. These results suggest that N-3389 acts as a 5-HT3 and 5-HT4 receptor antagonist.

- BRL 43694=Kytril® =Granisetron

Granisetronum INN (Granisetron)

1-Metyl-*N*-(*endo*-9-metyl-9-azabicyklo[3.3.1]non-3-yl)-1*H*-indazol-3--karboxamid



Selective and functional 5-hydroxytryptamine3 receptor antagonism by BRL 43694 (granisetron).; Sanger GJ, Nelson DR *Eur J Pharmacol* 1989 Jan 10, 159:2:113-24

The activity of BRL 43694 (granisetron) was investigated using established models of 5-HT3 receptor activity. In guinea-pig isolated ileum, BRL 43694 antagonised the contractions evoked by relatively high concentrations of 5-HT (pA2 = 8.1 +/- 0.2). However, except in high concentrations, BRL 43694 did not affect the contractions of similar preparations of ileum, evoked by electrical field stimulation (cholinergically mediated), the nicotinic agonist dimethylphenyl piperazinium (DMPP) or by cholecystokinin octapeptide. Similarly, BRL 43694 did not affect electrically evoked, cholinergically mediated contractions of rat or human isolated stomach. In other models of 5-HT3 receptor activity (rabbit isolated heart, Bezold-Jarisch reflex in anaesthetised rats), potent antagonism by BRL 43694 was demonstrated. In radioligand binding studies on rat brain membranes, BRL 43694 had little or no affinity for 5-HT1A, 5-HT1B, 5-HT2 or for many other binding sites. BRL

43694 may therefore be a potent and selective 5-HT3 receptor antagonist.

- Litoxetine=SL81.0385

Litoxetine: a selective 5-HT uptake inhibitor with concomitant 5-HT3 receptor antagonist and antiemetic properties. Angel I, Schoemaker H, Prouteau M, Garreau M, Langer SZ.; *Eur J Pharmacol* 1993 Mar 2, 232:2-3:139-45

The selective 5HT uptake inhibitor, litoxetine (SL 81.0385), currently under development as an antidepressant was shown to have antiemetic properties in the ferret. Litoxetine (at 1 and 10 mg/kg i.v.) dose dependently reduced the number of retches and vomiting as well as the number of emetic episodes induced by cisplatin (10 mg/kg i.v.) and delayed the onset of emesis. Fluoxetine (at 1 or 10 mg/kg i.v.) failed to inhibit cisplatin-induced emetic responses and, in contrast, significantly increased the number of retches and vomiting and accelerated the onset of emesis. The possibility that the antiemetic effects of litoxetine may be mediated through an interaction with 5HT3 receptors was studied using [3H]quipazine or [3H]BRL 43694 to label the 5HT3 receptor. Litoxetine has moderate affinity for cerebral 5HT3 receptors (Ki = 85 nM), while fluoxetine, similar to other 5HT uptake inhibitors, has only negligible affinity for this receptor (Ki = 6.5 microM). It is proposed that litoxetine inhibits cisplatin-induced emetic responses due to its moderate 5HT3 antagonist properties. The clinical use of the majority of serotonergic antidepressants (e.g. fluoxetine, fluvoxamine etc.) is associated with gastrointestinal discomfort (particularly nausea and vomiting) as a major side-effect. If nausea and vomiting associated

with the use of 5 HT uptake inhibitors are due to stimulation of 5HT3 receptors, the concomitant 5HT3 antagonism of litoxetine may limit the gastrointestinal side-effects of this novel antidepressant and thus offer an important advantage.

- LY 278584 ((1-methyl-N-(8-methyl-8-azabicyclo-[3.2.1.]oct-3-yl)-1H-indazole-3-carboxamide)

Specific [3H]LY278584 binding to 5-HT3 recognition sites in rat cerebral cortex.
Wong DT, Robertson DW, Reid LR; *Eur J Pharmacol* 1989 Jul 4, 166:1:107-10

Binding of [3H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT3 recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [3H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [3H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel their antagonism of the peripheral 5-HT3 receptors. Moreover, the order of potencies of other known antagonists of 5-HT3 receptors supports the conclusion that 3H]LY278584 binds to putative 5-HT3 receptors in cortical membranes.

- LY-278,584 maleate, see above.

- LY258-458

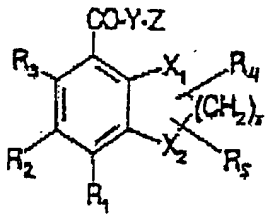
- LY 278989
Specific [3H]LY278584 binding to 5-HT3 recognition sites in rat cerebral cortex.
Wong DT, Robertson DW, Reid LR; *Eur J Pharmacol* 1989 Jul 4, 166:1:107-10

Binding of [3H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT3 recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [3H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [3H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel their antagonism of the peripheral 5-HT3 receptors. Moreover, the order of potencies of other known antagonists of 5-HT3 receptors supports the conclusion that [3H]LY278584 binds to putative 5-HT3 receptors in cortical membranes.

- LY-211-000

Benzofuranes,, benzooxazines, benzo(di)azepines, benso-thiazepines

A general structure for these classes of compounds is:



- 2,3-dihydro-benzofuran-7-carboxamides. X1=C, X2=O; five-membered ring system.

- RG 12915 ([4-[N-(1-azabicyclo[2.2.2.]octan-3-(S)-yl)]2-chloro-cis 5a-(S)-9a-(S)-5a,6,7,8,9,9a-hexahydrobenzofurancarboxamide hydrochloride])

- ADR 851 [4-amino-5-chloro-2,3-dihydro-N-(pyrrolidin-2-ylmethyl)benzofuran-7-carboxamide

- ADR-882
  Analgesic effects of S and R isomers of the novel 5-HT3 receptor antagonists ADR-851 and ADR-882 in rats.; Sufka KJ, Giordano J, *Eur J Pharmacol* 1991 Oct 29, 204:1:117-9

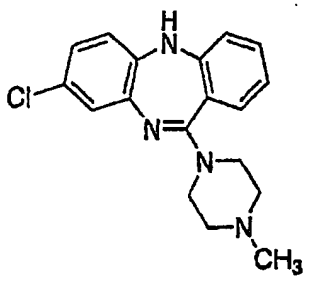
  The present study examined analgesia produced by S and R isomers of the novel 5-HT3 receptor antagonists, ADR-851 and ADR-882 (0.1-10 mg/kg s.c.) against acute thermal, mechanical and formalin-induced inflammatory pain in rats. Neither isomer of ADR-851 or ADR-882 was analgesic in the thermal or mechanical test. Similarly, neither S or R forms of ADR-882 produced significant anti-nociception in the formalin test. In contrast, ADR-851R produced significant analgesia at 3 and 10 mg/kg doses in this test, while ADR-851S produced significant analgesia only at 1 mg/kg.

- RP 62203 (2-[3-(4-(4-fluorophenyl)-piperazinyl)-propyl]naphto[1,8- ca]isothiazole-1,1-dioxide)

- Clozapine. Ingår i Leponex, Novartis

Clozapinum INN (Klozapin)

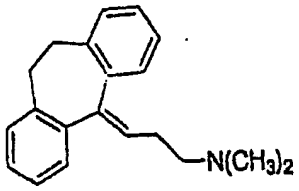
8-Kloro-11-(4-metyl-1-piperazinyl)-5*H*-dibenso[*b*,*e*][1,4]diazepin



- Amitryptiline

Amitriptylinum INN (Amitriptylin)

5-(3-Dimetylaminopropyliden)-10,11-dihydro-5*H*-
-dibens[*a*,*d*]cyklohepten



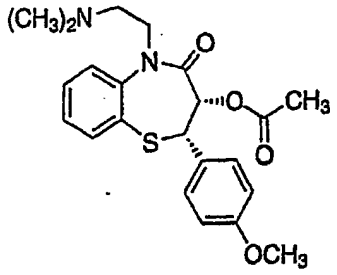
- Cyproheptadine. Is the active ingredient of Periactin, MSD

- Diltiazem

Is the active ingredient in Cardizem, Pharmacia Corporation

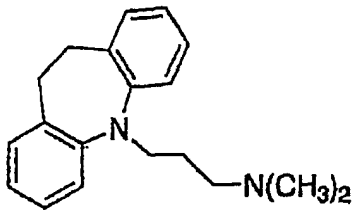
Diltiazemum INN (Diltiazem)

(2*S*,3*S*)-3-(Acetyloxi)-5-[2-(dimetylamino)etyl]-2-(4-metoxifenyl)-2,3-dihydro-1,5-bensotiazepin-4(5*H*)-on

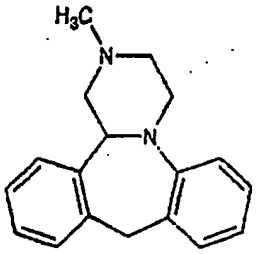


- Imipramin

5-(3-Dimetylaminopropyl)-10,11-dihydro-5*H*-dibenso[*b*,*f*]azepin



- Mianserin

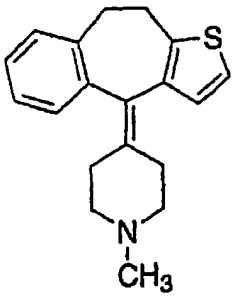


- Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methyl-. pyrazino[2,1-a] pyrido [2,3-c] benzazepine)

- Pizotifen

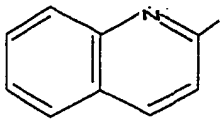
Pizotifenum INN (Pizotifen)

4-(1-Metyl-4-piperidyliden)-9,10-dihydro-4*H*-benso-[4,5]cyklohepta[1,2-*b*]tiofen



Quinolines, quinolicines and isoquinolines

The common structure of quinoline is:



Isoquinoline and quinolizine are isomers of quinoline.

- Quinoline-3-carboxamides

- Quinoline-4-carboxylates
- Isoquinoline-1-one (isomer till quinolin-1-one)
- SEC 579
- RS 56532 ((S)-6-amino-5-chloro-2-(1-azabicyclo-[2, 2, 2]octan-3-yl) 2,3-dihydro-1H-benz[de]-isoquinoline-1,3-dione hydrochloride)
- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile
- 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile
- KF 17643 (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-2-(n-propyloxy)-4-quinolinecarboxylate)
- KF 18259 ((endo-(8-methyl-8-aza- bicyclo[3.2.1]oct-3-yl)-1-isobutyl-2-oxo-1,2-dihydro-4-quinoline-carboxylate hydrochloride)
- KF 20170 (endo-N-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-4-hydroxy-3- quinolinecarboxamide
- Palonosetron=RS 25259-197 (3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]-isoquinoline-hydrochloride
- Quipazine (2-(1-piperazinyl)-Quinoline)
- N-metylquipazin
- 4-Ph-N-Me-quipazine

- RS-42358-197 [(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1 H-benzo[de]isoquinolin-1-one hydrochloride]

- RS-056812-198 (R)-N-(quinuclidin-3-yl)-2-(1-methyl-1 H-indol-3-yl)-2-oxo-acetamide

- RS-25259-197 [(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]-isoquinoline-hydrochloride)

The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, in vitro. Wong EH, Clark R, Leung E, Loury D, Bonhaus DW, Jakeman L, Parnes H, Whiting RL, Eglen RM, *Br J Pharmacol* 1995 Feb, 114:4:851-9

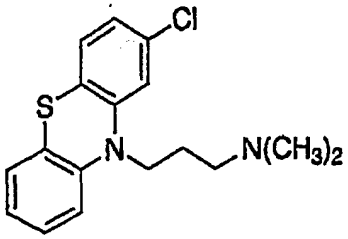
A series of isoquinolines have been identified as 5-HT3 receptor antagonists. One of these, RS 25259-197 [(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]isoquinoline-hydrochloride], has two chiral centres. The remaining three enantiomers are denoted as RS 25259-198 (R,R), RS 25233-197 (S,R) and RS 25233-198 (R,S). 2. At 5-HT3 receptors mediating contraction of guinea-pig isolated ileum, RS 25259-197 antagonized contractile responses to 5-HT in an unsurmountable fashion and the apparent affinity (pKB), estimated at 10 nM, was 8.8 +/-0.2. In this tissue, the -log KB values for the other three enantiomers were 6.7 +/- 0.3 (R,R), 6.7 +/- 0.1 (S,R) and 7.4 +/- 0.1 (R,S), respectively. The apparent affinities of RS 25259-197 and RS 25259-198, RS 25233-197 and RS 25233-198 at 5-HT3 receptors in membranes from NG-108-15 cells were evaluated by a [3H]-quipazine binding assay. The -log Ki values were 10.5 +/- 0.2, 8.4 +/- 0.1, 8.6 +/- 0.1 and 9.5 +/- 0.1, respec-

tively, with Hill coefficients not significantly different from unity. Thus, at these 5-HT3 receptors, the rank order of apparent affinities was (S,S) > (R,S) > (S,R) = (R,R). 3. RS 25259-197 displaced the binding of the selective 5-HT3 receptor ligand, [3H]-RS 42358-197, in membranes from NG-108-15 cells, rat cerebral cortex, rabbit ileal myenteric plexus and guinea-pig ileal myenteric plexus, with affinity (pKi) values of 10.1 +/- 0.1, 10.2 +/- 0.1, 10.1 +/- 0.1 and 8.3 +/- 0.2, respectively.

Phenthiazines and Benzoxazines

- Chlorpromazine

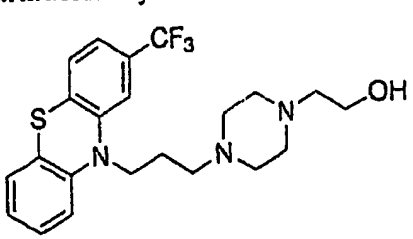
Chlorpromazinum INN (Klorpromazin)
10-(3-Dimetylaminopropyl)-2-klorofentiazin



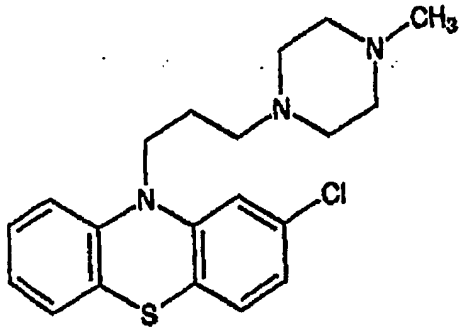
- Cyamemazine (10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile)

- Fluphenazin

Fluphenazinum INN (Flufenazin)
10-[3-(4-(2-Hydroxietyl)-1-piperazinyl)propyl]-2-trifluorometylfentiazin



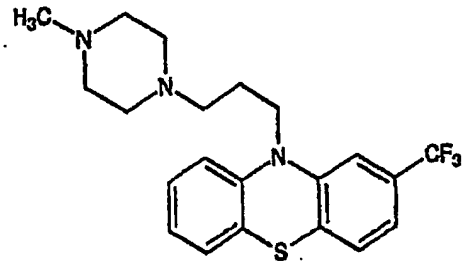
- Prochlorperazine=Stemetil



- KB-6933 (6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-piperazinyl)benzimidazole dimaleate)

- Perfenazine. Ingår i Trilafon. Cl istället för CF_3 i formeln för Flufenazine

- Trifluoperazine



- Azasetron=Y25130 (+/-)-N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide monohydrochloride

Pharmacokinetics of azasetron (Serotone), a selective 5-HT3 receptor antagonist.
Tsukagoshi S *Gan To Kagaku Ryoho* 1999 Jun, 26:7:1001-8

5-HT3 receptor antagonists have been established in a number of clinical trials as effective agents in the management of nausea and vomiting induced by cancer chemotherapy including cisplatin. Azasetron (Serotone) is a potent and selective 5-HT3 receptor antagonist, and classified as benzamide derivative. It has a different chemical structure from indole-type 5-HT3 receptor antagonists such as granisetron, ondansetron, ramosetron and tropisetron. The major difference is found in the pharmacokinetic profiles. Approximately 60-70% of azasetron administered i.v. and orally is excreted in urine as the unmetabolized form. Also, orally-administered azasetron has shown to be absorbed and/or secreted by the saturable transport mechanism in the small intestine, resulting in good bioavailability as approximately 90%. In this report, the relationship between the structure of 5-HT3 receptor antagonists (especially azasetron) and their pharmacokinetics were described.

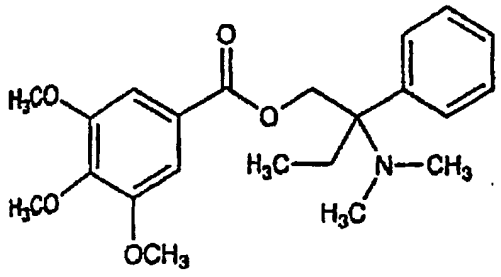
- 5-((Dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole

- 1,4-Benzoxazin-8-Carboxamide

Other compounds, including piperidines, piperazines, alkaloides, benzoates and ureas

- Anpirtoline (6-Chloro-2-[piperidinyl-4-thio]-pyridine)
- Ritanserin
- NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-butyl] piperazine)
- Naphtimides.
- TFMPP (1-(3-trifluoromethylphenyl)piperazine)

- Ifenprodil (dl-erythro-4-benzyl-alpha-(4-hydroxy-phenyl)-beta-methyl-1-piperidine-ethanol tartrate) (ifenprodil tartrate)
- MCPP (Meta-chlorophenylpiperazine) (mCPP)
- MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine)
- Metergoline ([[(8{BETA})-1,6-dimethylergolin-8-yl]methyl]-Carbamic acid phenylmethyl ester)
- Methysergide (1-methyl-D-lysergic acid butanolamide)
- S-apomorfin
- Tropanyl-3,5-dimethylbensoate
- Trimebutine, ett 3,4,5-trimetoxybensoate derivat.



- TMB-8 (8-(N,N-diethylamino)octyl 3,4,5-trimethoxy-benzoate)
- Phenylbiguanide

Functional characterization of a 5-HT3 receptor which modulates the release of 5-HT in the guinea-pig brain., Blier P, Bouchard C *Br J Pharmacol* 1993 Jan, 108:1:13-22

1. The aims of the present study were to confirm the modulation by 5-HT3 receptors of the electrically evoked release of tritium from slices preloaded with [3H]-5-HT of guinea-pig frontal cortex, hippocampus and hypothalamus, and to assess their functional role in 5-HT release. 2. The selective 5-HT3 agonist, 2-methyl-5-HT, introduced 8 min before the electrical stimulation, enhanced in a concentration-dependent manner the evoked release of [3H]-5-HT in the three brain regions studied. The 5-HT3 agonists, phenylbiguanide and m-chlorophenyl-biguanide, did not enhance the release of tritium in frontal cortex and hypothalamus slices. 3. In hypothalamus slices, this response was lost when 2-methyl-5-HT was introduced 20 min before the stimulation, thus indicating that these 5-HT3 receptors desensitize rapidly. When 2-methyl-5-HT was added 20-min before the first stimulation period to desensitize the 5-HT3 receptors, removed for 24 min, and then re-introduced 8 min before the second stimulation period, the enhancing effect of 2-methyl-5-HT was restored, thus indicating that these 5-HT3 receptors can rapidly regain normal sensitivity. 4. The enhancing effect of 2-methyl-5-HT was attenuated by the 5-HT3 receptor antagonists m-chloro-phenylpiperazine = quipazine = ondansetron > or = ICS 205-930 = BRL 24924 > MDL 72222 = zacopride. 5. The 5-HT reuptake blocker, paroxetine, enhanced the electrically evoked release of tritium when introduced 8 min before stimulation; this effect of paroxetine was blocked by ICS 205-930, thus indicating that these 5-HT3 receptors can be activated by endogenous 5-HT. 6. In the absence of electrical stimulation, 2-methyl-5-HT (10 microM) produced a marked enhancement of the basal release of [3H]-5-HT which was calcium-dependent and blocked by S-zacopride but not by paroxetine. 7. The enhancing effect of 2-methyl-5-HT was dependent both on

the frequency of stimulation, as indicated by the attenuated effect of 120 stimulations delivered at 1 Hz instead of 5 Hz, and on the duration of the stimulation, as indicated by the more pronounced effect of pulses delivered at 5 Hz for 24 s instead of 72 s or 120 s. McNeil-A-343 (4-(m-chlorophenylcarbamoyloxy)-2-butynyl-trimethylammonium chloride).

- MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate)

MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors., Fozard JR Naunyn Schmiedebergs *Arch Pharmacol* 1984 May, 326:1:36-44

The properties of MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate), a novel compound with potent and selective blocking actions at certain excitatory 5-hydroxytryptamine (5-HT) receptors on mammalian peripheral neurones, are described. On the rabbit isolated heart, MDL 72222 was a potent antagonist of responses mediated through the receptors for 5-HT present on the terminal sympathetic fibres. The threshold for antagonism was approximately 0.1 nM and the negative logarithm of the molar concentration of MDL 72222 which reduced the chronotropic response of the isolated rabbit heart to twice an ED50 of 5-HT to that of the ED50 was 9.27. MDL 72222 was also highly selective since responses to the nicotine receptor agonist, dimethylphenylpiperazinum iodine (DMPP), were inhibited only at concentrations more than 1000 times those necessary to inhibit 5-HT. In the anaesthetized rat, MDL 72222 produced marked blockade of the Bezold-Jarisch effect of 5-HT. Again, inhibition was selective since much higher doses of MDL 72222 failed to

alter the response to electrical stimulation of the efferent vagus nerves. In contrast, MDL 72222 proved only a weak and essentially non-selective antagonist of responses mediated by the 5-HT M-receptor present on the cholinergic nerves of the guinea-pig ileum. MDL 72222 does not block smooth muscle contractile responses elicited by oxytocin or mediated through 5-HT D-receptors, muscarinic or nicotinic cholinoceptors or histamine H1-receptors except at relatively high concentrations.

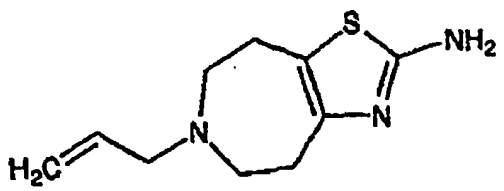
- MDL 72699 MDL 72699 är kvartenära saltet av MDL 72222..

- Mepyramine (N,N-dimethyl N'-(methoxy-4 benzyl)-N'-(pyridyl-2)ethylenediamine).

- Galanolactone= Gingerol.

The irregularly shaped roots (rhizomes) of ginger (*zingiber officinale*) are used extensively in Chinese, Indian, and Japanese cultures where they are believed to have anti-inflammatory, analgesic, cholesterol-lowering, and antithrombotic properties. Al-though ginger has been evaluated for the treatment of nausea and vomiting associated with hyperemesis gravidarum, anesthesia, and chemotherapy, this review will focus on ginger for motion sickness.

- Talipexole



Additional compounds

- YM 26103-2
- YM 26308-2
- M-840 ([[3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5- yl]-methyl]trimethyl-ammonium iodide)

Ref. A mechanism of 5-HT3 receptor mediation is involved etiologically in the psychological stress lesion the stomach of the mouse. , *J Pharmacol Exp Ther,* 1994 Oct, 271:1, 100-6

The role of brain amines, possibly involved in psychological stress, was evaluated and we postulate that the 5-hydroxytryptamine 5-HT3 receptors in the central nervous system are involved in the gastric lesion formation by psychological stress. The stress was in a communication box paradigm, in which each nonshocked mouse (responder) was placed in a Plexiglas compartment adjacent to mice receiving electrical shocks (sender). The responder mice revealed rather depressed gastric secretion, but developed gastric lesions which are significantly attenuated by pretreatment of dl-p-chlorophenylalanine methyl ester:HCl (PCPA; 200-400 mg/kg p.o.), but not 6-hydroxydopamine (6-OH-DA; 60 micrograms/body i.c.v. or 80 mg/kg i.p. 1 hr after a 20-mg/kg i.p. dose of desipramine). Oral treatment with GR38032F (0.01-1 mg/kg), ICS205-930 (0.01-20 mg/kg), MDL72222 (0.01-1 mg/kg), metoclopramide (0.1-100 mg/kg), ketanserin (0.01-10 mg/kg) and sulpiride (32-320 mg/kg) dose-dependently attenuated the psychological stress lesion formation, and the activity was arranged in the order of their in vitro binding affinities for the 5-HT3, but not 5-HT1A or 5-HT2 receptors. In contrast, a peripherally acting 5-HT3 antagonist, M-840 ([[3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5- yl]-methyl]trimethyl-ammonium io-

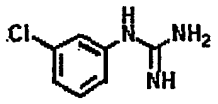
dide), dopamine acting compounds, haloperidol and FR64822 [N-(4-pyridylcarbamoyl)amino-1,2,3,6-tetrahydropyridine), and antisecretory drugs, atropine and famotidine, minimally affected the lesion formation.

- SDZ ICT 322, an indole-3-carboxylic acid scopine ester

- MD-354

MD-354. We were intrigued by the novel 5-HT3 agonist phenylbiguanide. It seemed quite selective for 5-HT3 receptors, but displayed rather low affinity (Ki >1,000 nM). In a prior study with Dr. S. Peroutka, we had investigated the SAFIR of various arylpiperazines at 5-HT3 receptors. Arylpiperazines, as mentioned earlier, are relatively nonselective agents; however, many bind at 5-HT3 receptors with significantly higher affinity that phenylbiguanide. We identified some structural similarities between the arylpiperazines and phenylbiguanide and, in collaboration with Milt Teitler, made a series of hybrid analogs that we hoped would bind with higher affinity than phenylbiguanide. Two such analogs were *meta*- chlorophenylbiguanide (*m*CPBG) and 2-naphthylbiguanide (Ki = 10-20 nM); both displayed significantly higher affinity than phenylbiguanide. Although we reported these compounds in abstract form, a full paper http://www.phc.vcu.edu/rag/serotonin/ - seven on *m*CPBG independently appeared by another group of investigators at the same time. It was not until a few years later that we finally published a full paper on these agents. However, in the course of our studies, we identified a novel class of 5-HT3 agonists: the arylguanides. MD-354, for example, was found to bind at 5-HT3 receptors with high affinity (Ki *ca.*

35 nM) and to display agonist actions in several assay systems.



MD-354

- S 21007 (21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine]).

Interaction of S 21007 with 5-HT3 receptors. In vitro and in vivo characterization.
Delagrange P, Emerit MB, Merahi N, Abraham C, Morain P, Rault S, Renard P, Pfeiffer B, Guardiola-Lemaître B,Hamon M; *Eur J Pharmacol* 1996 Dec 5, 316:2-3:195-203.

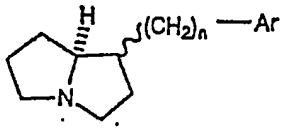
The interaction of S 21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine] with serotonin 5-HT3 receptors was investigated using biochemical, electrophysiological and functional assays. Binding studies using membranes from N1E-115 neuroblastoma cells showed that S 21007 is a selective high affinity (IC50 = 2.8 nM) 5-HT3 receptor ligand. As expected of an agonist, S 21007 stimulated the uptake of [14C]guanidinium (EC50 approximately 10 nM) in NG 108-15 cells exposed to substance P, and this effect could be prevented by the potent 5-HT3 receptor antagonist ondansetron. In addition, like 5-HT and other 5-HT3 receptor agonists (phenylbiguanide and 3-chloro-phenylbiguanide), S 21007 (EC50 = 27 microM) produced a rapid inward current in N1E-115 cells. The 5-HT3 receptor agonist

action of S 21007 was also demonstrated in urethane-anaesthetized rats as this drug (120 micrograms/kg i.v.) triggered the Bezold-Jarisch reflex (rapid fall in heart rate), and this action could be prevented by pretreatment with the potent 5-HT3 receptor antagonist zacopride. Finally, in line with its 5-HT3 receptor agonist properties, S 21007 also triggered emesis in the ferret. Evidence for 5-HT3 receptor antagonist-like properties of S 21007 was also obtained in some of these experiments since previous exposure to this compound prevented both the 5-HT-induced current in N1E-115 cells and the Bezold-Jarisch reflex elicited by an i.v. bolus of 5-HT (30 micrograms/kg) in urethane-anaesthetized rats. These data suggest that S 21007 is a selective 5-HT3 receptor agonist which can exhibit antagonist-like properties either by triggering a long lasting receptor desensitization or by a partial agonist activity at 5-HT3 receptors in some tissues.

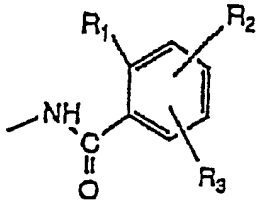
Further, in the following patent publications more compounds useful according to the present invention are presented.

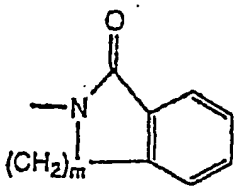
N-substituted benzamides

- EP0417746 (September 1990, G.D. Searle & Co) N-Azabicyclo/3.3.0/octane amides of aromatic acids. See also US5126343.

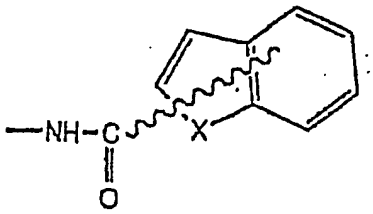


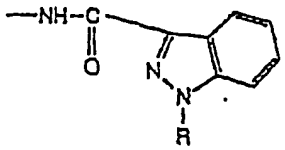
or a pharmaceutically acceptable salt thereof
wherein n is 0 or 1;
Ar can be

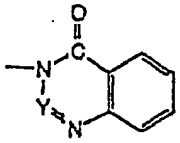




benzamide





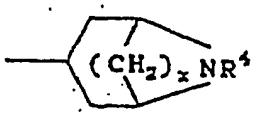


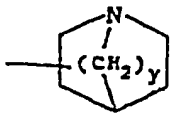
R^1 is alkoxy of 1 to 6 carbon atoms; and
R^2 and R^3 are the same or different and are hydrogen, halogen, CF_3, hydroxy, C_{1-6} alkoxy, C_{2-7} acryl, amino, amino substituted by one or two C_{1-6} alkyl groups, C_{2-7} acylamino, aminocarbonyl or aminosulfone, optionally substituted by one or two C_{1-6} alkyl groups, C_{1-6} alkyl sulfone or nitro groups;
wherein X can be NR, S, or O;
Y can be CH or N;
R is H, alkyl or aryl; and
m is 1 or 2.

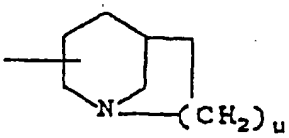
The structure is a benzamide with Ar=Ph-CONH-.

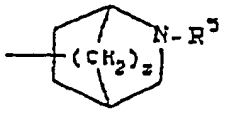
A compound of the formula or a pharmaceutically acceptable salt thereof wherein n is = or 1; and Ar is an aromatic amide moiety, which compound exhibits prokinetic activity and is a 5-HT3 antagonist.

- EP0430190 (November 1990, Syntex, Inc) New tricyclic compounds in which
the dashed line denotes an optional double bond;
n is 1, 2 or 3;
p is 0, 1, 2 or 3;
q is 0, 1 or 2;
each R^1 is independently selected from halogen, hydroxy, lower C_{1-6} alkoxy (optionally substituted with phenyl), lower C_{1-6} alkyl, nitro, amino. aminocarbonyl, (lower C_{1-6} alkyl)amino, di(lower C_{1-6} alkyl)amino, and (lower C_{1-6} alkanoyl)amino;
each R^2 is lower C_{1-6} alkyl; and
R^3 is selected from


(a)


(b)


(c)

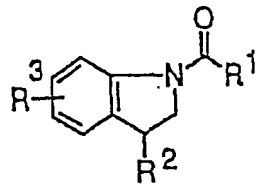

(d)

in which
u, x, y and z are all independently an integer from 1 to 3; and
R^4 and R^5 are independently C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR_6$ where t is 1 or 2 ant R_6 i thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl (optionally substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy); or
a pharmaceutically acceptable salt thereof or an N-oxide thereof; or
an individual isomer or mixture of isomers thereof.

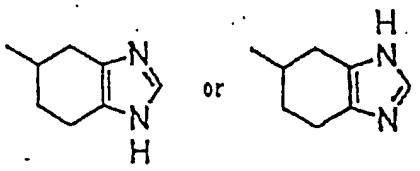
The present invention is directed to new pharmaceutically active compounds with 5-HT3 receptor antagonist activity of Formula I: in which the dashed line denoted an optional double bond; n is 1, 2 or 3; p is 0, 1, 2 or 3; q is 0, 1 or 2; each R1 is halogen, hydroxy, alkoxy (optionally substituted with phenyl), alkyl, nitro, amino, amino carbonyl, (alkyl)amino, di(alkyl)amino, and (alkanoyl)amino; each R^2 is alkyl; and R3 is in which u, x, y and z are all independently an integer from 1 to 3; and R4 and R5 are independently alkyl, cycloalkyl, cycloalkylalkyl, or a group (CH2)tR6 where t is 1 or 2 and R6 is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from alkyl, alkoxy, trifouoromehtyl or halogen, or is phenyl optionally substituted by alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and alkyl (optionally substituted).

Indoles, Indole-1-carboxamides and Imidazole derivatives

- EP0721949 (September 1993, Tokyo Tanabe Coompany Limited) Indoline compound and 5-HT3 receptor antagonist containing the same as active ingredient.



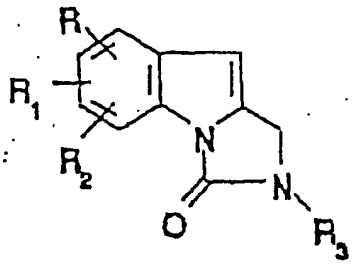
wherein R^1 represents the group



R^2 represents a phenyl group which may be substituted or an aromatic heterocyclic group, and R^3 represents hydrogen, a halogen, or a lower alkyl group, hydroxyl group, lower alkoxy group, carbamoyl group or lower alkoxycarbonyl group, or a physiologically acceptable salt thereof, or its solvate.

An indoline compound represented by general formula (I); a physiologically acceptable salt thereof; solvates of these compounds; and a 5-HT3 receptor antagonist containing the same as the active ingredient. In formula (I) R1 represents the group (a) or (b), R2 represents optionally substituted phenyl or heteroaryl; and R3 represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, carbamoyl or lower alkoxycarbonyl. The compound has a potent antagonism against 5-HT3 receptors in the intestinal tract as compared with the known 5-HT3 receptor antagonists and is excellent in the persistence of the activity. Hence it is useful for preventing or treating vomiting or nausea induced by chemotherapy or radiation, irritable bowel syndrome and diarrhea.

- EP0711299 (May 1994, Pharmacia S.p.A) Azabicycloalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One As 5HT 3 Antagonists

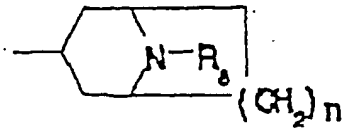


(I)

wherein

each of R, R_1 and R_2, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C_1-C_6 alkyl, CF_3, C_1-C_6 alkoxy, C_1-C_6 alkylthio, formyl, C_2-C_6 alkanoyl, carboxy, C_1-C_6 alkoxycarbonyl, nitro, -N(R_4 R_5) in which each of R_4 and R_5 independently is hydrogen, C_1-C_6 alkyl, formyl or C_2-C_6 alkanoyl; or a (R_6 R_7)N-SO_2 group, in which each of R_4 and R_7 independently is hydrogen or C_1-C_6 alkyl; R_3 is a group a)

or b)



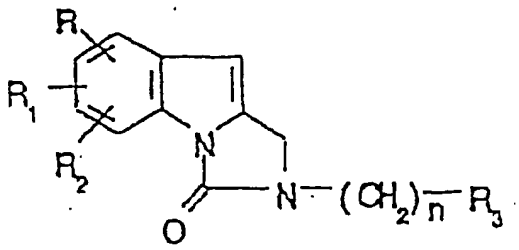
wherein

n is an integer of 1 or 2 and R_8 is hydrogen, C_1-C_6 alkyl unsubstituted or substituted by phenyl, C_2-C_4

alkenyl, C_2-C_4 alkynyl, formyl or C_2-C_6 alkanoyl; and the pharmaceutically acceptable salts thereof.

Novel 5-HT3 receptor antagonist compounds having general formula (I) wherein each of R, R1 and R2, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C1-C6 alkyl, CF3, C1-C6 alkoxy, C1-C6 alkylthio, formyl, C2-C6 alkanoyl, carboxy, C1-C6 alkyl-carbonyl, nitro, -N(R4 R5) in which each of R4 and R5 independently is hydrogen, C1-C6 alkyl, formyl or C2-C6 alkanoyl; or a (R6 R7)N-SO2 group, in which each of R6 and R7 independently is hydrogen or C1-C6 alkyl; R3 is a group (a) or (b) wherein n is an integer of 1 or 2 and R8 is hydrogen, C1-C6 alkyl unsubstituted or substituted by phenyl, C2-C4 alkenyl, C2-C4 alkynyl, formyl or C2-C6 alkanoyl; and the pharmaceutically acceptable salts thereof, are provided.

- EP0711293 (May 1994, Pharmacia S.p.A) Imidaxolylalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One And Their Use As Therapeutic Agents.



(I)

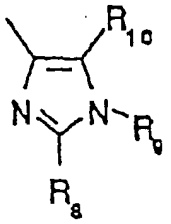
wherein

n, 1, 2 or 3 is;

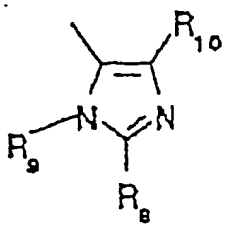
each of R, R_1 and R_2, which may be the same or different, is hydrogen, halogen, hydroxy, cyano C_1-C_6 alkyl, CF_3, C_1-C_6 alkoxy, C_1-C_6 alkylthio, formyl, C_2-C_6 alkanoyl, carboxy, C_1-C_6 alkoxycarbonyl, nitro, -N(R_4)R_5 in which each of R_4 and R_5 independ-

ently is hydrogen, C_1-C_6 alkyl, formyl or C_2-C_6 alkanoyl; or a $R_6(R_7)N$-SO_2 group, in which each of R_6 and R_7 independently is hydrogen or C_1-C_6 alkyl; R_3 is an imidazolyl group having the formula

a)



or b)

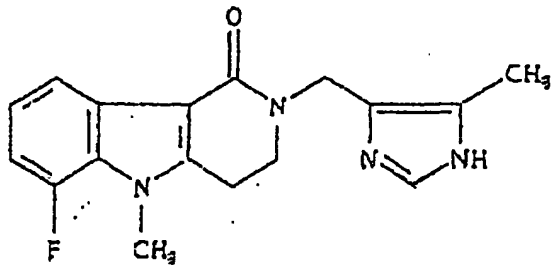


wherein each of R_6 and R_{10}, which may be the same or different, is hydrogen or C_1-C_6 alkyl, R_9 is hydrogen, C_1-C_6 alkyl or a nitrogen protection group chosen from triphenylmethyl, t-butyloxycarbonyl, benzyloxycarbonyl, acetyl, formyl, di(p-methoxyphenyl)-methyl and (p-methoxyphenyl)diphenylmethyl;
and the pharmaceutically acceptable salts thereof.

Novel 5-HT3 receptor antagonist compounds having formula (I), wherein n is 1, 2 or 3; each of R, R1 and R2, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C1-C6 alkyl, CF3, C1-C6 alkoxy, C1-C6 alkylthio, formyl, C2-C6 alkanoyl, carboxy, C1-C6 alkoxy-carbonyl, nitro, -N(R4 R5), in which each of R4 and R5 independently is hydrogen, C1-C6 alkyl, formyl or C2-C6 alkanoyl; or a (R6 R7)N-SO2 group, in which each of R6 and R7 independently is hydrogen or C1-C6 alkyl; R3 is an

imidazolyl group of formula (a) or (b), wherein each of R8 and R10 which may be the same or different is hydrogen or C1-C6 alkyl, R9 is hydrogen, C1-C6 alkyl or a nitrogen protecting group; and the pharmaceutically acceptable salts thereof, are disclosed.

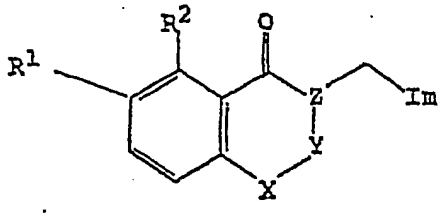
- EP0581388 (July 1993, Glaxo Group Ltd) Pyridoindolone Methansulphonate as 5HT and 5HT3 receptor antagonists.



(I)

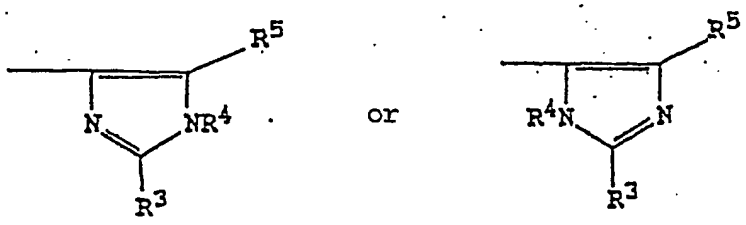
This invention relates to the novel salt 6-fluoro-2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one methane sulphonate, to solvates of this salt, to pharmaceutical compositions containing it and to its use in medicine as 5-HT3 receptor antagonists.

- EP0364274 (October 1989, Glaxo Group Ltd) Imidazole derivatives.



(I)

wherein Im represents an imidazolyl group of the formula:



and one of the groups represented by R^3, R^4 and R^5 is a hydrogen atom, or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl C_{1-3} alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

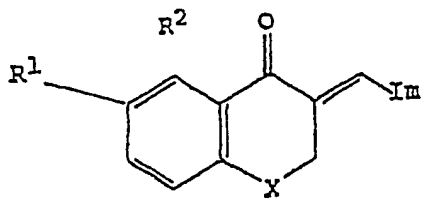
R^1 and R^2 each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring;

X represents an oxygen or a sulphur atom, or a group NR^6, wherein R^6 represents a C_{1-6} alkyl group;

Z-Y represents the group $CH-CH_2$ or C=CH;

and physiologically acceptable salts and solvates thereof, which comprises:

(A) for the production of a compound of formula (I) in which Z-Y represents the group $CH-CH_2$, hydrogenating a compound of formula (II):



(II)

or a protected derivative thereof, followed if necessary by removal of any protecting groups present; or

(B) for the production of a compound of formula (I) in which Z-Y represents the group C=CH, reacting a compound of formula (II), or a protected derivative thereof, with an organic acid or a mineral acid, followed if necessary by removal of any protecting groups present; or

(C) converting a compound of general formula (I) into another compound of formula (I) using conventional techniques; or

(D) removing protecting group(s) from a protected form of a compound of formula (I);

and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer;

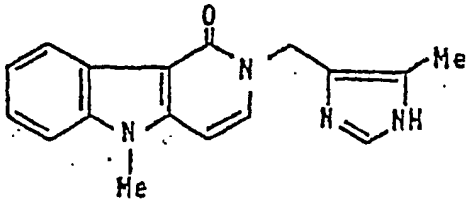
and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

The invention provides imidazole derivatives of the general formula (I) wherein Im represents an imidazolyl group of the formula: and one of the groups represented by R3, R4 and R5 is a hydrogen atom, or a C1-C6 alkyl, C3-7 cycloalkyl, C3-6 alkenyl, phenyl or phenyl C1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C1-6 alkyl group; R1 and R2 each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring; X represents an oxygen or a sulphur atom, or a group NR6, wherein R6 represents a C1-6 alkyl group; Z-Y represents the group CH-CH2 or C=CH; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytrypta-

mine at 5-HT3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety and nausea and vomiting.

- EP0392663 (March 1989, One Pharmaceutical Co Ltd) Carboline derivative as a 5-HT3 receptor antagonist.

A γ-carboline of the formula I



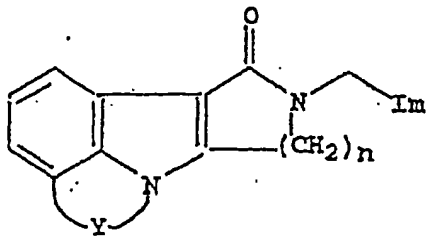
I

or pharmaceutically acceptable acid addition salt and/or hydrate thereof for use in a method of treatment or prophylaxis of diseases or conditions induced by the action of 5-hydroxytryptamine on 5-hydroxytryptamine 3-receptors in a mammal, including man.

The present invention provides γ-carbolines of the formula: or non-toxic acid additional salts thereof and/or hydrates thereof, for use as 5-HT3 receptor antagonists. The present invention also provides pharmaceutical compositions comprising compounds of the formula I.

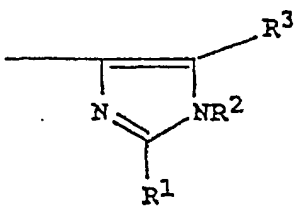
- EP0357417 (August 1989, Glaxo Group Ltd) Lactam derivatives.

Compounds of the general formula (I)

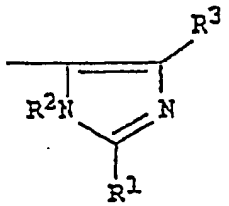


(I)

wherein n represents 2 or 3;
Im represents an imidazolyl group of the formula:



or



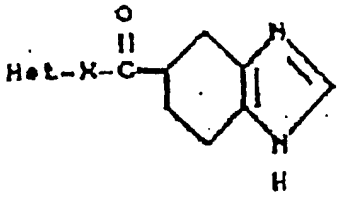
wherein one of the groups represented by R^1, R^2 and R^3 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl C_{1-3} alkyl-group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;
Y represents a group $-(CH_2)_{m-}$, wherein m represents 2, 3 or 4; or Y represents a group $-X(CH_2)_{p-}$, C_{1-6} alkyl group, and X is attached to the benzene ring moiety of the molecule;
and physiologically acceptable salts and solvates thereof.

The invention provides lactam derivatives of the general formula (I) wherein n represents 2 or 3; Im

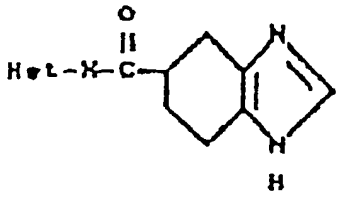
represents an imidazolyl group of the formula: wherein one of the groups represented by R1, R^2 and R3 is a hydrogen atom or a C1-6 alkyl, C3-7 cycloalkyl, C3-6 alkenyl, phenyl or phenyl C1-3 alkyl-group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C1-6 alkyl group; Y represents a group -(CH2)m-, wherein m represents 2, 3 or 4; or Y represents a group -X(CH2)p-, wherein p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR4, where R4 is a C1-6 alkyl group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT3 receptors and are useful, for example in the treatment of psychotic disorders, anxiety and nausea and vomiting.

- RU2059623 Tetrahydrobenzimidazole derivatives or its pharmaceutically acceptable salt.

tetrahydrobenzimidazole derivative of the formula



and a pharmaceutical composition containing an effective amount of compound

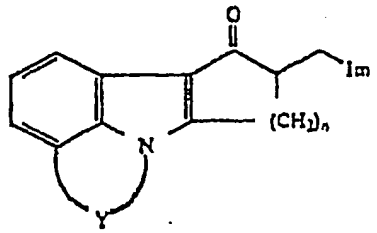


and a pharmaceutically

acceptable carrier showing activity of a 5-HT3 receptor antagonist.

- US5,045,545 (May 1989, Glaxo Group Limited) [(Imidazol-4(and 5)-yl)methyl] tetracyclic ketones having 5-HT_3 antagonist activity.

The invention relates to tetracyclic ketones of the general formula (I)



(I)

wherein

n represents 1, 2 or 3;

Im represents an imidazolyl group of the formula:

wherein one of the groups represented by R^1, R^2 and R^3 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl C_{1-3} alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

Y represents a group $-(CH_2)_{m-}$, wherein m represents 2, 3 or 4; or a group $-X(CH_2)_{p-}$, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR^4, where R^4 is a C_{1-6} alkyl group, and X is attached to the benzene ring moiety of the molecule;

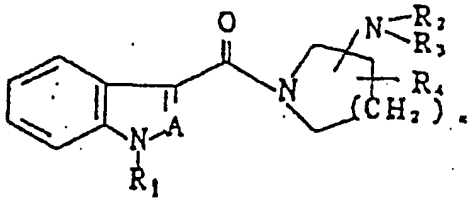
and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT_3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

The invention relates to tetracyclic ketones of the general formula (I)##STR1## wherein n represents 1, 2 or 3; Im represents an imidazolyl group of the formula: ##STR2## wherein one of the groups represented by R.sup.1, R.sup.2 and R.sup.3 is a hydrogen atom or a C.sub.1-6 alkyl, C.sub.3-7 cycloalkyl, C.sub.3-6 alkenyl, phenyl or phenyl C.sub.1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C.sub.1-6 alkyl group; Y represents a group --(CH.sub.2)m--, where m represents 2, 3 or 4, or a group -X(CH.sub.2).sub.p--, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR.sup.4, where R.sup.4 is a C.sub.1-6 alkyl group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT.sub.3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

Indazole carboxamide derivatives

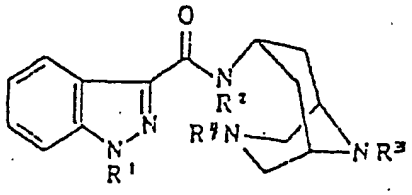
- EP0630893 (March 1992, Kyorin Pharmaceutical Co., Ltd.) N,N'-Disubstituted Amide Derivative.



(I)

A 5-HT3 antagonist containing a novel N,N'-disubstituted amide derivative having a potent and selective 5-HT3 receptor antagonism, represented by general formula (I), a hydrate thereof, or an acid addition salt thereof, wherein R1 represents hydrogen or lower alkyl; R2 and R3 may be the same or different from each other and each represents hydrogen, lower alkyl, lower alkenyl, aryl-substituted lower alkyl which may be substituted, acyl or lower alkoxycarbonyl; R4 represents hydrogen, lower alkyl or lower alkoxy; A represents CH or N; and n represents 1, 2 or 3.

- EP0558923 (January 1992, Nisshin Flour Milling Co., Ltd.) Diazabicyclo derivatives as 5-HT3 antagonists



(I)

wherein

R^1 is alkyl, 3-methyl-2-butenyl, cyclopropylmethyl, 2-propynyl, cyanomethyl, 2-oxopropyl, 2-hydroxypropyl, 2-pyridylmethyl, methoxycarbonylmethyl, 2-ethoxyethyl, isobutoxycarbonyl, or 4,6-diamino-2-triazinylmethyl;

R^2 is hydrogen; and

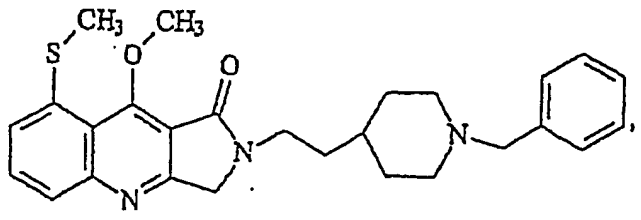
R^3 and R^4 are methyl.

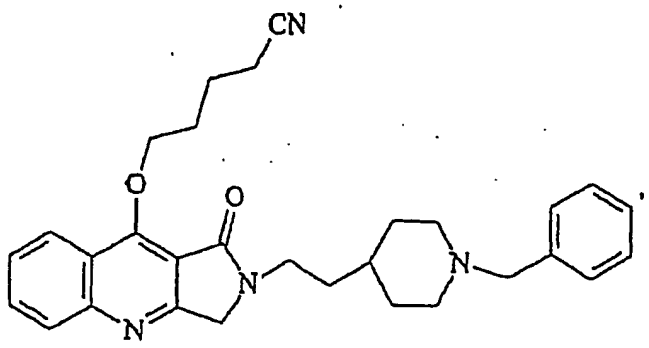
Diazabicyclo derivatives of formula (I) and pharmaceutically acceptable salts thereof: wherein R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, oxoalkyl, alkoxycabonylalkyl, alkoxycarbonyl, acyl, dialkylaminoalkyl, hydroxyalkyl, haloalkyl, cyanoalkyl, heterocycloalkyl, aryl, heteroarylalkyl or arylalkyl, the aryl group and the aryl moiety being optionally substituted by alkoxy, nitro, alkyl, amino or halo; R^2 is hydrogen or alkyl; R3 and R4 may be the same or different and each is hydrogen, alkyl, alkenyl, acyl, alkoxyalkyl or arylalkyl wherein the aryl moiety is optionally substituted by alkoxy, nitro, alkyl, amino or halo; with the proviso that when R^2 is hydrogen and both R3 and R4 are methyl, R1 does not represent hydrogen, alkyl, unsubstituted benzyl or dimethylaminoethyl; having 5-HT3 receptor antagonist activity.

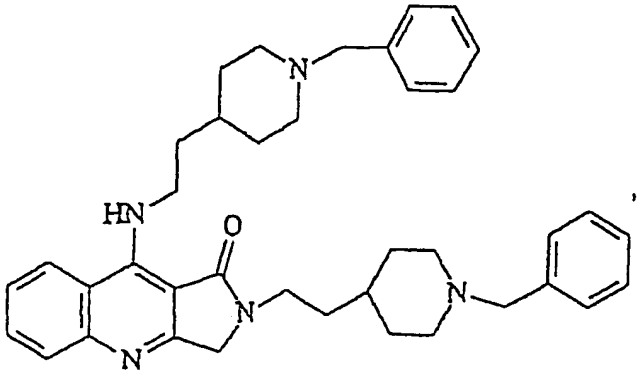
Quinolines and Isoquinolines

- WO9964421 (June 1999, Arena Pharmaceuticals, Inc) Acetylcholine enhancers.

An acetylcholine enhancer selected from the group consisting of the chemical compounds represented by the following structures:



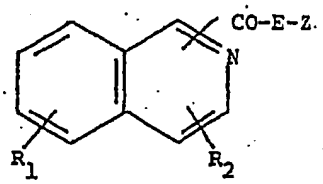




Disclosed herein are quinoline derivatives having dual mechanistic properties, referred to in this patent documents as "acetylcholine enhancers", i.e., compounds which evidence acetylcholinesterase (AChE) inhibition activity, and 5-HT3 receptor antagonist activity. A particularly preferred compound is 2-[2-(1-benzylpiperizin-4-yl)ethyl]-2,3-dihydro-9-methoxy-1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate, referred to herein as Compound A ("Cm.A").

- EP0526545 (April 1991, Beecham Group p.l.c.) Isoquinoline Amides And Esters As 5-HT3 Receptor Antagonists.

A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

E is NH or O,

R_1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy or nitro;

Z is an azacyclic or azabicyclic side chain; and

i) the group CO-E-Z is in the 1-position and either R_2 is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_2 is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by oone or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

ii) the group CO-E-Z is in the 3-position and either R_2 is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_2 is in the 4-position and is hydrogen or C_{1-6} alkoxy;

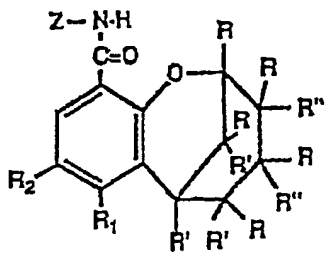
having 5-HT_3 receptor antagonist activity.

Isoquinoline derivatives (I) having 5-HT3 receptor antagonist activity, a process for their preparation and their use as pharmaceuticals. In formula (I) E

is NH or O, R1 is hydrogen, halogen, alkyl, alkoxy, hydroxy or nitro; Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c) wherein; p is 1 or 2; q is 1 to 3; r is 1 to 3; R3 or R4 is hydrogen or alkyl, and Y is a group -CH2-X-CH2- wherein X is -CH2-, oxygen, sulphur or X is a bond; and (I) when the group CO-E-Z is in the 1-position and either R2 is in the 3-position and is hydrogen, alkyl, or alkoxy, or R2 is in the 4-position and is hydrogen CF3, alkyl, acyl, acylamino (substituted) phenyl or (substituted) amino, (substituted) aminocarbonyl or (substituted) aminosulphonyl; (II) the group CO-E-Z is in the 3-position and either R2 is in the 1-position and is hydrogen, alkyl or alkoxy or R2 is in the 4-position and is hydrogen or alkoxy.

- EP0628043 (February 1992, Merrell Dow Pharmaceutical Inc) 2,6-Methano-2H-Quinolizin As 5-HT3-Receptor Antagonist

A compound of the formula:



where

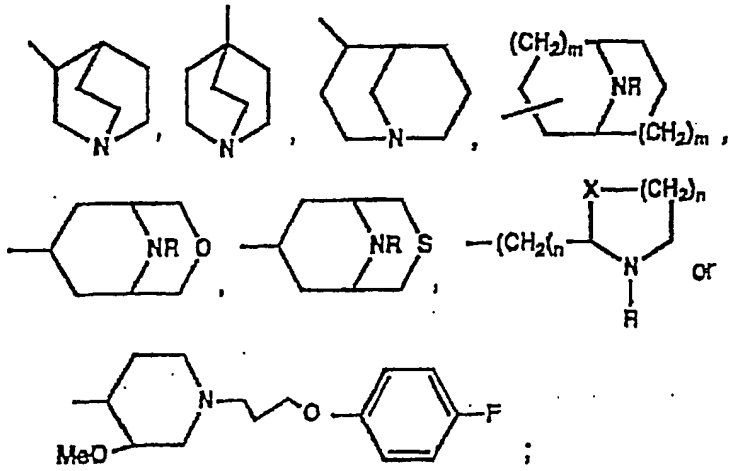
R is hydrogen or alkyl;

R_1 is hydrogen, amino, mono- and di-alkylamino, acylamino, halo or haloalkyl;

R_2 is hydrogen, halo, sulfamyl, mono- and di-alkylsulfamyl or haloalkyl;

R' and R" are independently hydrogen or alkyl;
vicinal R' and/or R" groups may form a C=C double bond;
geminal R and R' and R and R" groups may be $-(CH_2)_n-$ where n is 2 to 6;

Z is

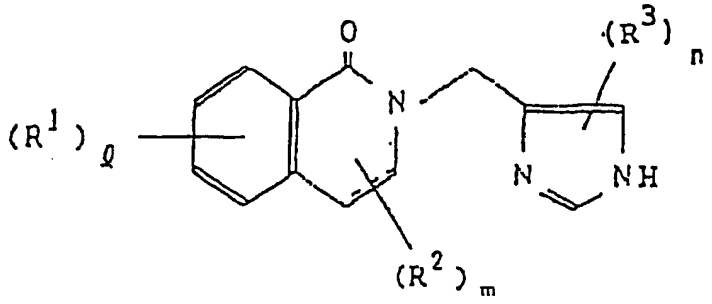


where m is 0-2, n is 1-2 and X is N or S; or pharmaceutically acceptable salts thereof.

This invention relates to 5-chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid-octahydro-3-hydroxy-2,6-methano-2H-quinolizin-8-yl ester (I), a novel 5-HT3-receptor angatonist, its method of preparation, and to its end-use application in the treatment of radio- and chemo-therapeutically-induced nausea and vomiting, in the treatment of pain associated with migraine, in the treatment of cognitive disorders, in treating hallucinatory en-

dogenous psychoses of the type manifested in patients suffering from schizophrenia and mania, for irritable bowel syndrome, and to combat drug abuse.

- EP0482939 (October 1991, Ono Pharmaceuticals) Isoquinolinone derivative.



wherein each substituent R^1 is the same or different and is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or a group of formula:

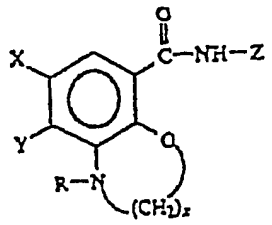
$-NR^4R^5$

wherein R^4 is hydrogen, C_{1-4} alkyl or C_{2-4} alkanoyl and R^5 is hydrogen, C_{1-4} alkyl or benzyl;
each substituent R^2 is the same or different and is hydrogen or C_{1-4} alkyl;
each substitutent R^3 is the same or different and is hydrogen or C_{1-4} alkyl;
l is 1, 2, 3 or 4;
m is 1 or 2;
n is 1 or 2 and
=== is a single bond or double bond; or a non-toxic acid addition salt thereof or a hydrate thereof.

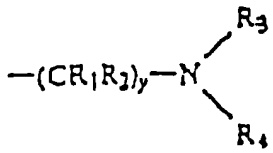
Isoquinolinone derivatives of the formula: wherein R1 is hydrogen, C1-4 alkyl, C1-4 alkoxy or a group of formula: -NR4R5 wherein R4 is hydrogen, halogen, C1-4 alkyl or C2-4 alkanoyl and R5 is hydrogen, C1-4 alkyl or benzyl; R^2 is hydrogen or C1-4 alkyl; R3 is hydrogen or C1-4 alkyl; l is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2 and --- is a single bond or double bond an non-toxic acid addition salts thereof and are useful for the prevention and/or treatment of diseases induced when 5-HT acts on 5-HT3 receptors (especially vomiting induced by the administration of an anti-cancer agent).

Benzofuranes, Benzooxazines and Benzo(di)azepines

- US4935511 (September 1989, Rorer Pharmaceutical Corporation) Benzoxazine benzooxazipine carboxamide 5-HT3 antagonists.



where
X is hydrogen, halo, sulfamyl, alkylsulfamyl or alkylsulfonyl;
Y is hydrogen, amino, mono- or di-alkylamino or halo;
Z is



3-quinuclidine, 4-quinuclidine, 4-(1-azabicyclo-[3.3.1]nonane), 3-(9-methylazabicyclo[3.3.1]nonane) or 4-[3-methoxy-1-(3(-[4-fluorophenoxy]propyl)piperidine];
R, R_1, R_2, R_3 and R_4 are independently: hydrogen or alkyl;
x is 2 or 3;
y is 1 to 4;
and pharmaceutically acceptable salts thereof.

This invention relates to benzoxazine and benzoxazepine carboxamide compounds which exhibit 5-HT.sub.3 antagonist properties including CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D.sub.2 receptor binding affinity. This invention also relates to pharmaceutical compositions and methods for the treatment of gastrointestinal and mental disorders using said compounds.

- IL 107654 Use of substituted N-3,4-dihydro-4-oxo-2-2-pyrimidyl)amino alkyl-4-piperidinyl 2,2-dimethyl-7-benzofuran and benzopyrancarboxamide.

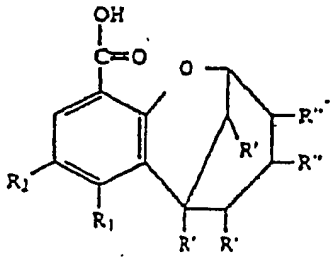
A pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof, wherein
R1 and R2 represent hydrogen, or
R1 and R2 taken together from a bivalent radical of formula
-CH=CH-CH=CH-(a)
-CH=C(Cl)-CH=CH-(b) or
-CH=CH-C(Cl)=CH-(c);
n represents 2, 3 or 4;
R3 represents hydrogen or methoxy;
m represents 1 or 2;

R4 represents hydrogen, amino or C1.3alkylcarbonyl-amino; and

R5 represents hydrogen or halo,

for the manufacture of a medicament for treating 5-HT3-mediated disorders.

- US5288731 (August 1992, Rhone-Poulenc Rorer Pharmaceuticals Inc)2,6-Methano-2H-1-Benzoxacincarboxylic acids, esters and amides.



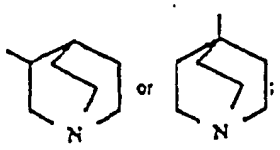
and its steroisomers, enantiomers, diasteroisomers and racemic mixtures with an amine of the formula H_2N-Z;

where

R_1 is hydrogen, an amino or alkylamino optionally substituted with a protecting group halo or haloalkyl;

R_2 is hydrogen, halo, sulfamyl, mono- and di-alkylsulfamyl or haloalkyl;

R′ and R″ are hydrogen or alkyl; and Z is:



and its racemic mixtures and stereospecific isomers.

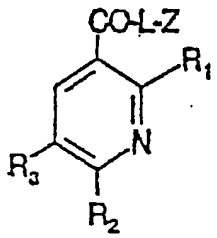
Novel compounds which are 2,6-methano-2H-1-benzoxocincaboxamides having 5-HT.sub.3-antagonist properties including unique CNS, antiemetic and gastric prokinetic activities and which are void of any significant D.sub.2 receptor binding affinity, therapeutic compositions and methods of treatment of disorders which result from 5-HT.sub.3 activity using said compounds. Processes for their preparation and the preparation of their intermediates are also disclosed.

- WO9209284 2,6-Methano-2-H-1-benzoxacincarboxamides as 5-HT3 antagonists.

Other 5-HT3 antagonist compounds

- EP0611370 (October 1992, Smithkline Beecham Plc) Pyridine-3-Carboxylic Acid Esters Or Amides Useful As 5-HT3 Antagonists.

A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is C_{1-6} alkoxy, C_{3-8} cycloalkoxy or C_{3-8} cycloalkyl C_{1-4} alkoxy;

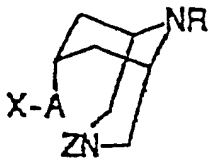
R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino optionally substituted by one or two C_{1-6} alkyl groups;

R_3 is hydrogen, halo or C_{1-6} alkyl;
L is O or NH; and
Z is a di-azacyclic or azabicyclic side chain;
having 5-HT_3 receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof wherein R1 is C1-6 alkoxy, C3-8 cycloalkoxy or C3-8 cycloalkyl C1-4 alkoxy; R2 is hydrogen, halo, C1-6 alkyl, C1-6 alkoxy or amino optionally substituted by one or two C1-6 alkyl groups; R3 is hydrogen, halo or C1-6 alkyl; L is O or NH; and Z is a di-azacyclic or azabicyclic side chain; having 5-HT3 receptor antagonist activity.

- EP0607233 (October 1991, Smithkline Beecham Plc)3,9-Diazabicyclo(3.3.1)Nonane Derivatives With 5-HT3 Receptor Antagonist Activity

A compound of formula (I), or a pharmaceutically acceptable salt thereof:



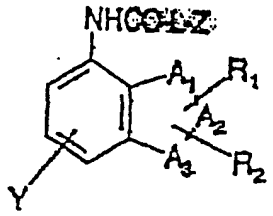
(I)

wherein
X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;
A is a linking moiety;
Z is a carboxylic acyl group; and
R is hydrogen or methyl;
having 5-HT_3 receptor antagonist activity.

Compounds of formula (I), and pharmaceutically acceptable salts thereof, wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is a linking moiety; Z is a carboxylic acyl group; and R is hydrogen or methyl; having 5-HT3 receptor antagonist activity.

- WO9308185 (January 1991, Smithkline Beecham Plc)N-Aryl-N1-Azabicyclo-Ureas As 5-HT3 Antagonists

A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

A_1, A_2, A_3 and the carbon atoms to which they are attached form a 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-;

R_1 and R_2 are hydrogen or C_{1-6} alkyl;

Y is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

L is O or NH;

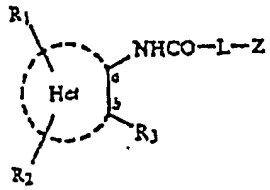
Z is an azabicyclic side chain;

having 5-HT_3 receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein A1, A2 , A3 and the carbon atoms to which they are attached form a 5- or 6-membered non-aromatic heterocyclic ring containing

at least one -O-, -CO- or -N-; R1 and R2 are hydrogen or C1-6 alkyl; Y is hydrogen, halo, C1-6 alkyl or C1-6 alkoxy; L is O or NH; Z is an azabicyclic side chain; having 5-HT3 receptor antagonist activity.

- US4808588 (July 1987, Beecham Group) Heterocyclic ureas and carbonates useful as pharmaceuticals.



(I)

wherein

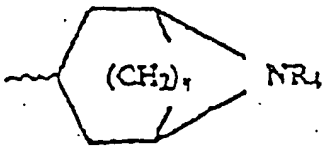
Het is monocyclic heteroaryl having two adjacent carbon atoms, a and b, depicted in formula (I) selected from the group consisting of pyridine, pyrimidine, pyrazine, pyrrole, imidazole, thiophene, furan, oxazole and thiazole;

R_1 and R_2 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl and C_{1-6} alkoxy;

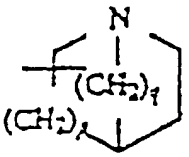
R_3 is hydrozy, C_{1-6} alkoxy, C_{3-7} alkenyl-methoxy, phenoxy or phenyl C_{1-4} alkoxy in which either phenyl moiety may be substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halo; CO_2R_6 wherein R_6 is hydrogen or C_{1-6} alkyl, $CONR_7R_8$ or $SO_2NR_7R_8$ wherein R_7 and R_8 are independently hydrogen or C_{1-6} alkyl or together are C_{4-6} polymethylene, NO_2, $(CH_2)_mOR_9$ wherein m is 1 or 2 and R_9 is C_{1-6} alkyl or $S(O)_nR_{10}$ wherein n is 0, 1 or 2 and R_{10} is C_{1-6} alkyl;

L is NH or O;

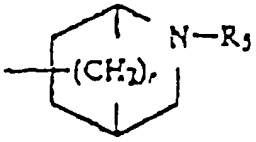
Z is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_4 or R_5 is C_{1-4} alkyl.

Compounds of formula (I), or a pharmaceutically acceptable salt thereof: ##STR1## wherein: Het is monocyclic heteroaryl having two adjacent carbons atoms, a and b, depicted in formula (I); p1 R.sub.1 and R.sub.2 are independently selected from hydrogen, halogen, CF.sub.3, C.sub.1-6 alkyl and C.sub.1-6 Alkoxy; R.sub.3 is hydroxy, C.sub.1-6 alkoxy, C.sub.3-7 alkenyl-methoxy, phenoxy or phenyl C.sub.1-4 alkoxy in which either phenyl moiety may be substituted by one or two C.sub.1-6 alkyl, C.sub.1-6 alkoxy or halo; Co.sub.2 R.sub.6 wherein R.sub.6 is hydrogen or C.sub.1-6 alkyl, CONR.sub.7 R.sub.8 or SO.sub.2 NR.sub.7 R.sub.8 wherein R.sub.7 and R.sub.8 are independently hydrogen or C.sub.1-6 alkyl or together are C.sub.4-6 polymethylene, NO.sub.2, (CH.sub.2).sub.m OR.sub.9 wherein m is 1

or 2 and R.sub.9 is C.sub.1-6 alkyl or S(O).sub.n R.sub.10 wherein n is 0, 1 or 2 and R.sub.10 is C.sub.1-6 alkyl; L is NH or O; Z is a group of formula (a), (b) or (c); ##STR2## wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R.sub.4 or R.sub.5 is C.sub 1-4 alkyl; having 5-HT.sub.3 antagonist activity, a process for their preparation and their use as pharmaceuticals.

The most preferred 5-HT_3 receptor antagonists for the present indications are tropanyl 3,5-dimethylbenzoate, MDL 72222, SDZ 216-525, ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron, and Cilansetron.

Brief Description of the Drawing

Fig. 1 depicts the effects of 5-HT and the selective 5-HT_4 agonist RS 67333 on the spontaneous tone in a human airway preparation in vitro. Note that 5-HT only gives a transient relaxation, while the selective 5-HT_4 agonist causes a strong sustained relaxation effect.

Detailed Description of the Invention

As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT_4 receptor, this sustained relaxing effect is achieved because the contractile 5-HT_3 receptor is not affected; only the relaxing 5-HT_4 receptor is activated. In the case of antagonists to the 5-HT_3 receptor, this effect is achieved due to direct blocking of the 5-HT_3 receptor, whereby the unspecific agonists to the 5-HT_4 receptor, such as 5-HT, can act without also causing contraction by the 5-HT_3 receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may op-

tionally include two or more of the above outlined compounds.

Further, in the embodiment when the compound having 5-HT_3 antagonist activity is administered, optionally together with complementary serotonin or derivatives thereof, a serotonin uptake inhibitor can be added with a view to amplifying the relaxing effect, e.g. fluoxetin, citalopram, paroxetine, sertralin, and fluvoxamine.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, intramuscular, intrathecal, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Moreover, said medicament is preferably administered via the respiratory tract in the form of *e.g.* an aerosol or an air-suspended fine powder. However, in some cases useful alternative administration forms are tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories.

The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the

thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S. Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and this oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead displays a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from a specific type of airway epithelium cells, so called neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin (5-HT), which activiates 5-HT_1, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 as well as 5-HT_2 receptors, in particular 5-HT_2, 5-HT_3, and 5-HT_4 receptors.

Additional experiments have shown that when a small dose (1 μM) serotonin (5-HT) was added to denuded guinea-pig airway smooth muscle preparations displaying a strong, smooth spontaneous tone, the average force level was increased significantly, *i.e.* a transient contraction was observed. A contractile effect of serotonin (5-HT) on airways (smooth muscle) has previously been reported, see *e.g.* Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, 86:789-798, 1999. However, when a large dose (100 μM) of 5-HT was used, the spontaneous tone was, after a transient contraction, significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal pre-treatment level when the preparations were again exposed to control, drug-free conditions. Thus, it has now surprisingly been shown that serotonin causes a contraction of guinea-pig airways at

low concentrations and relaxation at high concentrations, i.e. a dual effect.

Similar experiments have also been performed on human airway preparations from patients undergoing lobectomy or pulmectomy due to lung cancer. In humans, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig: even as low a concentration as 1 μM 5-HT induced a significant relaxation in preparations displaying a spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro preparations have shown that 5-HT indeed causes a contraction also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline (pre-treatment). The relaxation, which has a maximum after 10-15 min, disappears gradually during the following 30-45 min (see Fig 1). In guinea pig trachea, the first 5-HT-induced effect is a contraction which reaches a maximum after approximately 10 min, and this is followed, within approximately 30 min, by a considerable reduction of tone, i.e. a relaxation below the pre-treatment level. The transient nature of the 5-HT relaxation in human airways is most likely caused by a simultaneous activation of the fast relaxing 5-HT_4 receptor, and an activation of the slower contracting receptor, which in human airways surprisingly has been found to be the 5-HT_3 receptor. This is clear, because activation of the relaxing 5-HT_4 receptor by a substance that lacks 5-HT_3 receptor activating properties (such as RS 67333), results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. sero-

tonin, may be of use as an addition to standard beta2 receptor stimulation for the treatment of acute asthma attacks. However, from the presently described experiments it seems clear that 5-HT alone is unsuitable, i.e. not effective or useful, for the treatment of said diseases, e.g. asthmatic disorders, because of the only transient relaxing effect by 5-HT (see Fig. 1). Also, reports from other groups indicate that 5-HT if anything tends to induce a weak bronchoconstriction rather than a relaxation in asthmatics (see e.g. Dupont et al. 1999, Eur Resp J 14:642-649 and Takahashi et al. 1995, Am J Respir Crit Care Med 152:377-380, which are incorporated herein by reference).

In summary, it has now been discovered that agonist action on the 5-HT_4 receptor results in a relaxing effect, whereas agonist action on 5-HT_3 receptors results in a contractile effect. In conclusion, the dual effect of 5-HT is most likely a result of its agonist action on the relaxing 5-HT_4 receptor as well as on the contracting 5-HT_3 receptor.

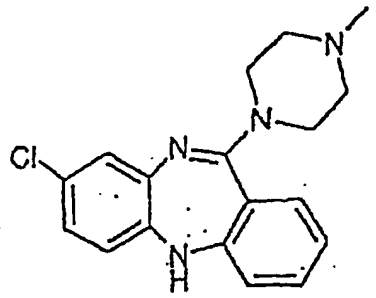
It was also deduced from these experiments that compounds having agonist activity to the 5-HT_4 receptor, while having only low or no agonist activity to a 5-HT_3 receptor, therefore are useful as agents for treatment of disorders involving airway constriction, as defined above.

In the above mentioned experiments it has been shown that compounds having antagonist activity to a 5-HT_3 receptor are useful as agents for treatment of disorders involving airway constriction, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT_3 receptor. Administration of serotonin, a serotonin reuptake inhibitor or any other substance having 5-HT_4 receptor agonist activity results in increased relaxation of the bronchi.

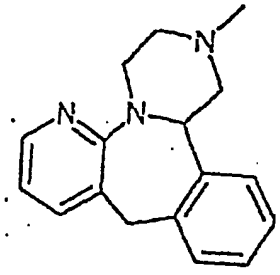
CLAIMS

1. Compound having antagonist activity to a 5-HT_3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor for use as a medicament for treatment of disorders involving airway constriction.

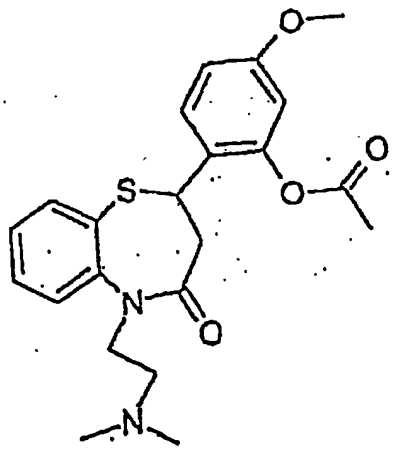
2. Compound according to claim 1, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising



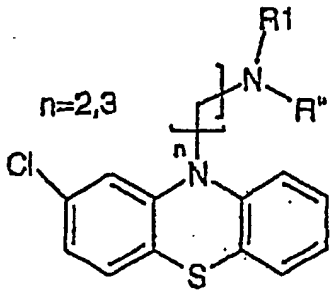
benzazepines, preferably mirtazapine



benztiazephines, preferably diltiazem

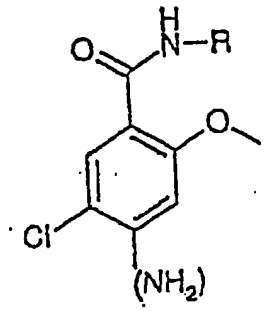


and fentiazines



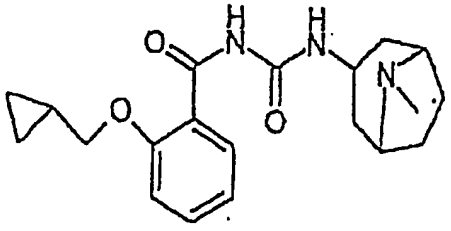
preferably perphenazine, chlorpromazine, stemetil;

compounds also having 5-HT_4 receptor agonist activity, preferably benzamides



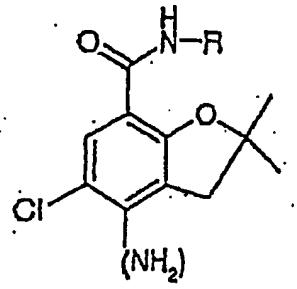
(cisapride, zacopride, mosapride, metoclopramide, pancopride, BRL 24924, BMY 33462)

and



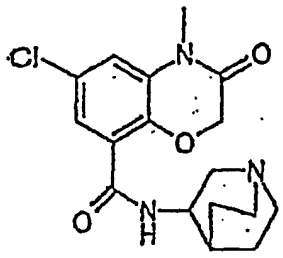
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



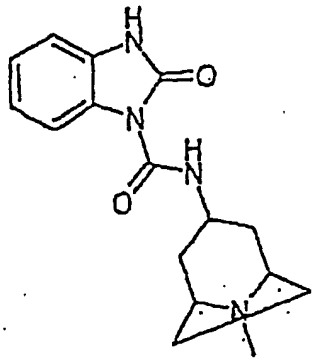
(preferably zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides



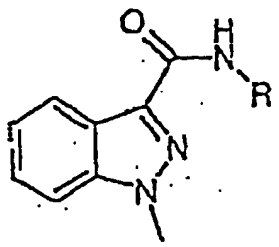
preferably azasetron (=Y25130);

benzimidazolones



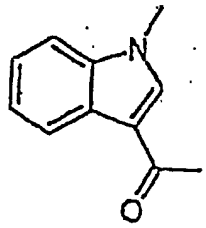
preferably itasetron (=DAU 6215);

indazol-3-carboxamides

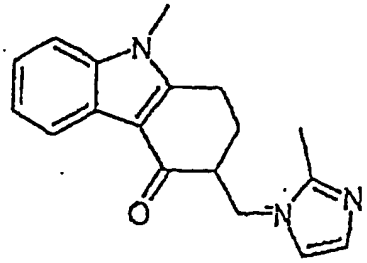


preferably N 3389, LY 278584, DAT 582 (=(R)AS-5370);

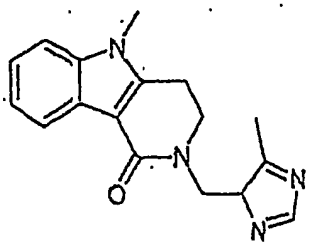
wherein the latter group reminds most of the specific 5-HT_3 antagonists, which contains the group



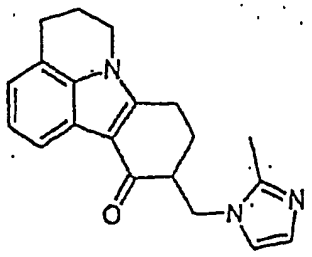
in different forms, such as



ondansetron

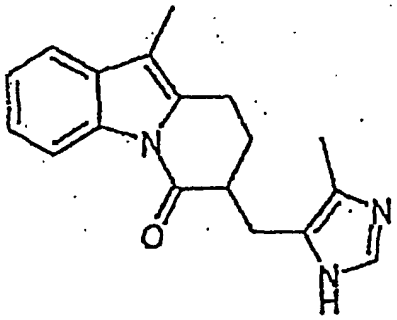


alosetron



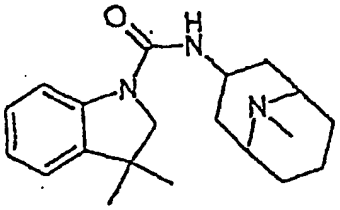
cilansetron (=KC 9946)

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen



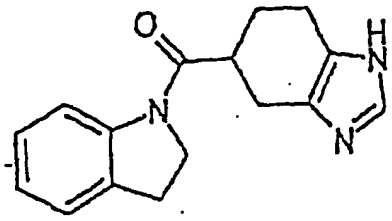
FK 1052

also being an antagonist against both 5-HT_3 and 5-HT_4 receptors,



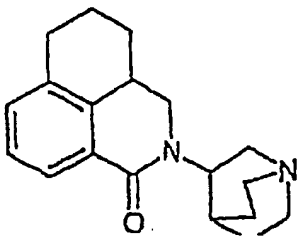
BRL 46470 A

bisindoles

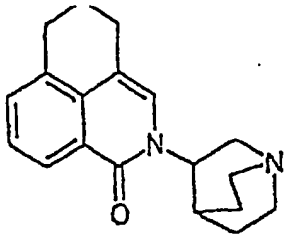


YM 114

isoquinoline-1-ones

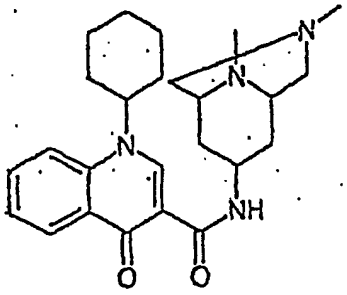


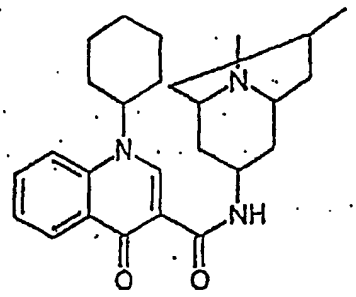
palonosetron (=RS 25259-197)



RS 42358-197

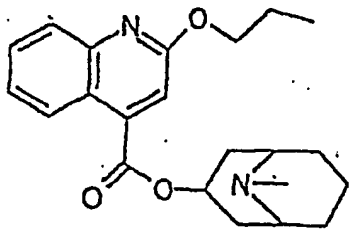
and the quinoline-3-carboxamides



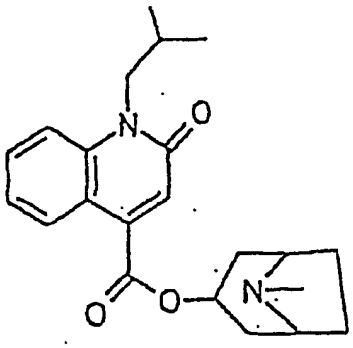


WAY-SEC 579 Mirisetron (=WAY 100579);

quinoline-4-carboxylates

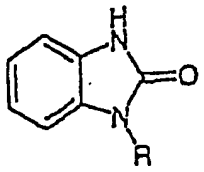


preferably KF 17643

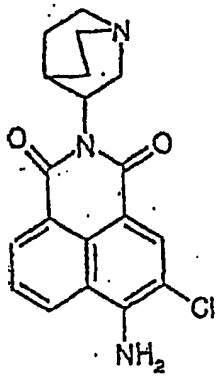


preferably KF 18259;

benzimidazolones



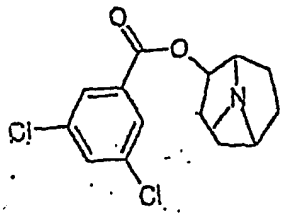
preferably droperidol (neurolidol), itasetron (DAU6215), and the naphtimides



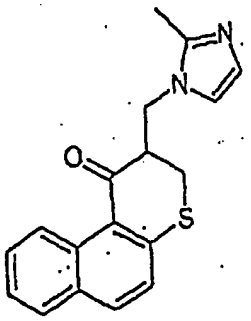
RS 56532

preferably RS 56532;

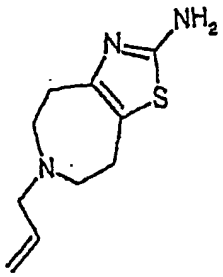
MDL 72222, which also is a specific 5-HT_3 antagonist;



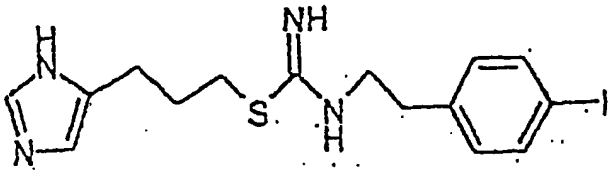
; and



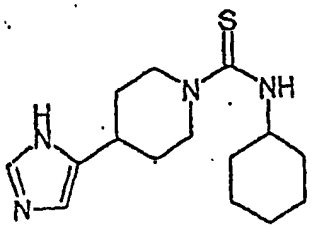
GK 128



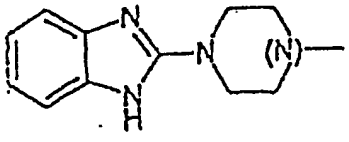
Talipexole



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Imipramine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Pancopride, Phenylbiguanide, Pitozifen, Prochlorperazine (Stemetil), QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-25259-197, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron (=ICS 205-930 =Rifenserin), Bemesetron, L-683,877, LY-278,584 maleate and derivatives and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect.

3. Compound according to claim 3, wherein it preferably is tropanyl 3,5-dimethylbenzoate, MDL 72222,

SDZ 216-525, ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron and Cilansetron.

4. Compound according to claim 3, wherein said airway constriction appears in asthma, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, preferably asthma.

5. Use of one or more of the compounds according to any of claims 1-3, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction, (optionally together with a serotonin uptake inhibitor).

6. Use according to claim 5, wherein said one or more compounds has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

7. Use according to any one of claims 5 and 6, wherein said disorder involving airway constriction is asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, preferably asthma.

8. A method for treatment of disorders involving airway constriction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claims 1-3.

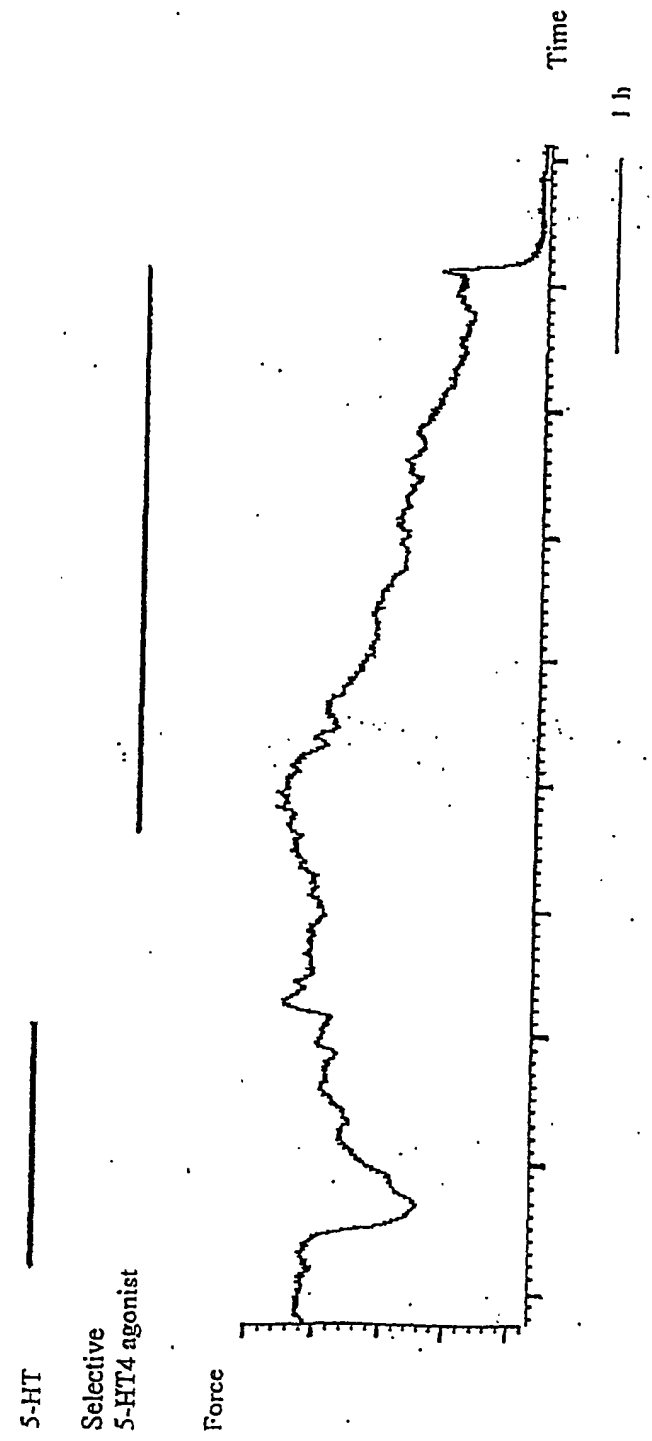


Fig 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02613

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61K 31/4045, A61P 11/06, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 8904660 A1 (BEECHAM GROUP PLC), 1 June 1989 (01.06.89) --	1-8
X	WO 9112254 A1 (NOVO NORDISK A/S), 22 August 1991 (22.08.91), page 1, line 18 - line 24 --	1,5-8
P,X	WO 0064441 A1 (RESPIRATORIUS AB), 2 November 2000 (02.11.00), see claims --	1-8
E,X	WO 0076500 A2 (RESPIRATORIUS AB), 21 December 2000 (21.12.00), see particularly claims 8-12 --	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2001	21 -05- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02613

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,X	WO 0110423 A2 (NOVARTIS AG), 15 February 2001 (15.02.01)	1-8
	--	
X	Am J Respir Crit Care Med, Volume 152, 1995, Tsuneyuki Takahashi et al, "5-Hydroxytryptamine Facilitates Cholinergic Bronchoconstriction in Human and Guinea Pig Airways" page 377 - page 380	1-8
	--	
X	Neuropharmacology, Volume 37, 1998, Deborah J. Bootle et al, "The role of central 5-HT receptors in the bronchoconstriction evoked by inhaled capsaicin in anaesthetised guinea-pigs" page 243 - page 250	1-8
	--	
X	Eur Respir J, Volume 14, 1999, L.J. Dupont et al, "The effects of 5-HT on cholinergic contraction in human airways in vitro" page 642 - page 649	1-8
	--	
X	The Journal of Pharmacology and Experimental Therapeutics, Volume 257, No 1, 1991, Carl K. Buckner et al, "A Pharmacologic Examination of Receptors Mediating Serotonininduced Bronchoconstriction in the Anesthetized Guinea Pig" page 26 - page 34	1-8
	--	
X	Am J Respir Crit Care Med, Volume 157, 1998, Christopher J. Meade, "The Mechanism by Which Epinastine Stops an Adenosine Analog from Contracting BDE Rat Airways" page 522 - page 530	1-8
	--	
X	European Journal of Pharmacology, Volume 180, 1990, Thomas P. Blackburn, "Pharmacological studies in vivo which ICI 169,369 a chemically novel 5-HT2/5-HT1C receptor antagonist" page 229 - page 237	1-8
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02613

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	British Journal of Anaesthesia, Volume 78, 1997, N. Otoma et al, "In vivo assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope" page 579 - page 582	1,2,5-8
X	Lille Médical, Volume 16, No 5, 1971, F. Guerrin et al, "Effets du métroclapramide sur le bronchospasme expérimental du cobaye et sur le test á l'acétylcholine chez l'homme" page 731 - page 735	1,2,5-8
X	European Journal of Pharmacology, Volume 6, 1969, Enrique Hong et al, "Similarities between the pharmacological actions of quipazine and serotonin" page 274 - page 280	1,2,5-8
X	J. Pharmacobio-Dyn., Volume 12, 1989, Yoshio Tsuchiya, "Inhibition of the vagal reflex-induced tracheal constriction by psychotropic drugs" page 437 - page 440	1,2,5-8
X	Anesth Analog, Volume 72, 1991, Benoit Gentil et al, "Droperidol Prevents Serotonin-Induced Bronchospasm in the Guinea Pig" page 612 - page 615	1,2,5-8

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/SE00/02613

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 1-2,5-8
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*

Claim 8 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

**

Claim 1 and depending parts of claims 5-8 relate to compounds defined by reference to a desirable characteristic or property, namely that the compounds are having antagonist activity to the 5-HT3 receptor. The mentioned claims cover all compounds having this characteristic or property. Claim 2 (which is dependent of claim 1) and depending parts of claims 5-8 are restricted to specific compounds. However, these claims relate to a very great number of structurally different compounds whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, claims 1-2 and 5-8 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Further, expressions such as "compound having antagonist activity to a 5-HT3 receptor" and "disorders involving airway constriction" are not clear and concise. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has mainly been carried out for those parts which appear to be clear, supported and disclosed, namely claims 3-4 and those parts of claims 5-8 relating to claim 3.

The applicant's attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/04/01

International application No.
PCT/SE 00/02613

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8904660 A1	01/06/89	AT 78162 T	15/08/92
		AU 616706 B	07/11/91
		AU 2626488 A	14/06/89
		DE 3872872 A,T	20/08/92
		DK 345889 A	12/07/89
		EP 0340270 A,B	08/11/89
		SE 0340270 T3	
		GB 8726716 D	00/00/00
		JP 2502185 T	19/07/90
		US 5098909 A	24/03/92
		GB 8726717 D	00/00/00
WO 9112254 A1	22/08/91	AT 156128 T	15/08/97
		AU 648066 B	14/04/94
		AU 7340991 A	03/09/91
		CA 2074803 A	17/08/91
		DE 69127072 D,T	22/01/98
		DK 40890 D	00/00/00
		EP 0515537 A,B	02/12/92
		SE 0515537 T3	
		FI 923475 A	31/07/92
		IE 910523 A	28/08/91
		IL 97429 A	31/01/96
		JP 5504358 T	08/07/93
		NO 923194 A	14/08/92
		NZ 237122 A	25/02/93
		PT 96788 A,B	31/10/91
		US 5187164 A	16/02/93
		US 5290795 A	01/03/94
		ZA 9101103 A	27/11/91
WO 0064441 A1	02/11/00	AU 5259100 A	10/11/00
		AU 5895099 A	27/03/00
		SE 9901531 D	00/00/00
		AU 1429400 A	22/05/00
		SE 9901906 D	00/00/00
		AU 2016000 A	03/07/00
		SE 9902251 D	00/00/00
		WO 0076500 A	21/12/00
		AU 2016100 A	19/06/00
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		AU 5259100 A	10/11/00
		SE 9902251 D	00/00/00
		WO 0064441 A	02/11/00
		AU 2016100 A	19/06/00
		SE 9902252 D	00/00/00
		SE 0000819 D	00/00/00
WO 0110423 A2	15/02/01	GB 9918425 D	00/00/00